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(54) QUINAZOLINE-3-ALKANOIC ACID DERIVATIVE, SALT THEREOF, AND PRODUCTION THEREOF

QUINAZOLIN-3-ALKANCARBONSÄUREDERIVAT UND SALZ UND DEREN HERSTELLUNG

DERIVE DE L'ACIDE QUINAZOLINE-3-ALCANOIQUE, SELS DERIVES DE CE COMPOSE ET SA PRODUCTION

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- **CHEMICAL ABSTRACTS, vol. 107, 1987, page 46, abstract no. 168619k, Columbus, Ohio, US; A.R. EL NASSER OSSMAN et al.: "Synthesis and anticonvulsant activity of some new 2,4-(1H,3H)-quinazolinedione derivatives", & BULL PHARM. SCI., ASSIUT UNIV. 1986, 9(1), 105-18**
- **EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 25, 1990, pages 121-126, Paris,**
- **FR; F. BILLON et al.: "Aldose reductase inhibition by 2,4-oxo and thioxo derivatives of 1,2,3,4-tetrahydroquinazoline"**

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Description

Technical field

The present invention relates to novel quinazoline-3-alkanoic acid derivatives having inhibitory effects on platelet aggregation and aldose reductase activity, their salts, their preparation processes and medicinal drugs containing them.

Background techniques

Recently, it has been made clear that the platelets and the arachidonic acid metabolites play an important role for the origin of thrombotic diseases such as cardiac infarction and the prevention therefrom, and the development of useful drugs therefor such as inhibitory agent of platelet aggregation is expected. On the other hand, with the diabetic neuropathy and complications of diabetes mellitus, the participation of aldose reductase has been made clear, thus the inhibition of the activity of aldose reductase will be connected with the therapy and the prevention of complications originating from diabetes mellitus.

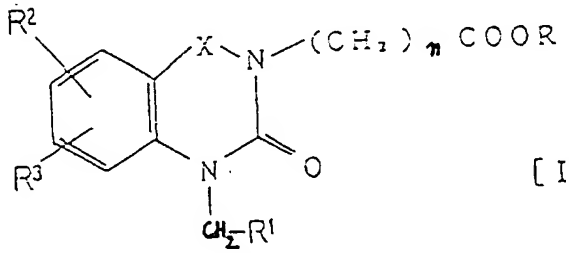
Chem. Abs. 107, 1987 Abs. No. 16819k discloses quinazoline-3-alkanoic acid derivatives having anticonvulsant activity. However, in said derivatives, the substituent in 1-position cannot be a benzyl group.

Compounds having inhibitory effect on platelet aggregation or compounds having inhibitory effect on aldose reductase are widely searched separately. For example, the fact that quinazoline-1-alkanoic acid derivatives have the inhibitory effect on aldose reductase is disclosed in Japanese Unexamined Patent Publication No. Sho 62-96476, No. Hei 1-125322 and No. Hei 1-131164, but these compounds have no inhibitory effect on platelet aggregation. The quinazoline-3-alkanoic acid derivatives of the invention are novel compounds, and any prior art to allow to presume that the compounds of the invention have both the inhibitory effect on platelet aggregation and the inhibitory effect on aldose reductase cannot be found.

The purpose of the invention is to provide useful compounds as medicinal drugs having excellent inhibitory effect on aldose reductase together with strong inhibitory effect on platelet aggregation.

Disclosure of the invention

As a result of diligent studies to solve such problem, the inventors have found that quinazoline-3-alkanoic acid derivatives represented by a general formula (I)



[I]

wherein R is hydrogen or a protecting group for the carboxyl group, R^1 is a phenyl group which may be substituted by one to three of lower alkyl group having 1 to 6 carbon atoms, lower alkoxy group having 1 to 3 carbon atoms, halogen, trifluoromethyl group, carboxyethylene group or ethoxycarbonylethylene group, R^2 and R^3 which are identical or different from each other, each represents hydrogen, halogen, lower alkyl group having 1 to 6 carbon atoms, lower alkoxy group having 1 to 3 carbon atoms, aralkyl group, nitro group, imidazolyl group, imidazolylmethyl group or

(R^4 and R^5 which are identical or different from each other, each represents hydrogen or lower alkyl group having 1 to 6 carbon atoms, or are connected with each other to form a five- or six-membered heterocyclic group which may contain other hetero atoms), X is a carbonyl or thiocarbonyl group, and n indicates an integer of 1 to 3, and the compounds: Ethyl 6-(2,4-dichlorobenzyloxy)-1-(2,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-3(2H)quinazoline acetate and 6-(2,4-dichlorobenzyloxy)-1-(2,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-3(2H)quinazoline acetic acid or their salts have excellent inhibitory effect on platelet aggregation and strong inhibitory effect on aldose reductase, leading to the completion of the invention.

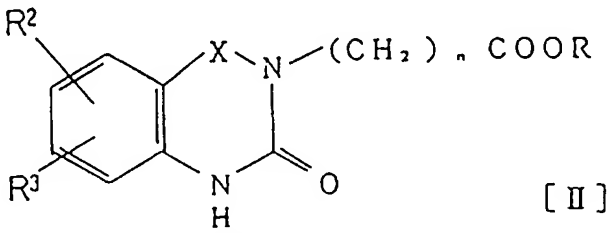
As "lower alkyl" shown in the invention, straight chain or branched one with carbon atoms of 1 to 6 such as methyl,

ethyl, n-propyl or isopropyl can be mentioned. As "lower alkoxy", one with carbon atoms of 1 to 3 such as methoxy, ethoxy, n-propoxy or isopropoxy can be mentioned. As "halogen", fluorine, chlorine, bromine or iodine can be mentioned.

As "five-membered or six-membered heterocycle combined R^4 and R^5 one another, which may contain additional hetero atoms", for example, pyrrolidinyl, piperidino, morpholino, thiazolidyl or imidazolyl can be mentioned. "Heterocycle" means a saturated or unsaturated, monocyclic or polycyclic heterocyclic group capable of containing one or more oxygens, sulfurs and nitrogens and, for example, pyridyl, imidazolyl, thienyl, or isoxazolyl, can be mentioned. As the "protecting group for carboxyl group", lower alkyl, alkyl bearing phenyl group which may be substituted, alkoxyalkyl, hydroxyalkyl, tetrahydrofuranyl, tetrahydropyranyl or pivaloyloxymethyl can be mentioned. "Eliminating group" shown by Z is halogen (e.g. chlorine, bromine or iodine) or substituted sulfonyloxy (e.g. methanesulfonyloxy or benzenesulfonyloxy) or hydroxy and preferable one is halogen. "Their salts" in the invention mean salts permissible as medicinal drugs and salts with cations such as sodium, potassium, calcium or magnesium. Moreover, some ones among the compounds of the invention show amphoteric property. In such cases, their salts can include salts with inorganic acids (e.g. hydrochloric acid or sulfuric acid) or with organic acids (e.g. p-toluenesulfonic acid or acetic acid).

According to the invention, compounds of the general formula [I] can be prepared through the processes shown below.

1-a) Compounds represented by the general formula [I] can be obtained by reacting compounds represented by the general formula [II]



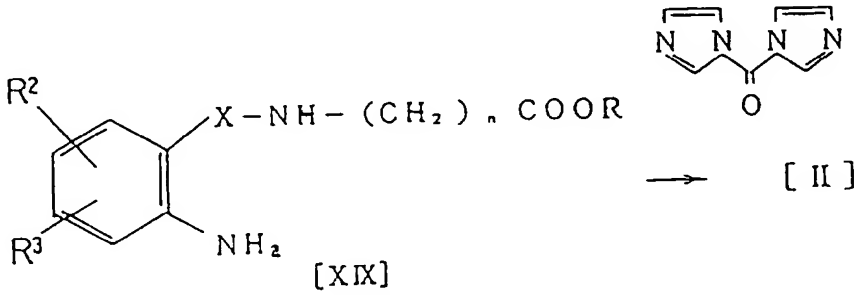
[II]

[wherein R, R^2, R^3, X and n are as described above], with compounds represented by the general formula [III]

$$R^1\text{-}CH_2\text{-}Z \qquad [III]$$

[wherein Z indicates an eliminating group and R^1, is as described above],
in the presence of a suitable base. This reaction can be conducted advantageously in a solvent such as ethanol, dimethylformamide or dimethyl sulfoxide and in the presence of alkali metal hydride such as, for example, sodium hydride, lower alkoxide such as, for example, sodium ethoxide, alkali metal hydroxide such as, for example, sodium hydroxide, alkali metal carbonate such as, for exmaple, potassium carbonate or organic base such as, for example, pyridine, triethylamine or the like as a base. At this time, adding of catalytic amount to equimolar amount of alkali metal iodide such as sodium iodide is advantageous in order to promote the reaction. The reaction temperature is made to be within a range of 50 to 120 °C and the reaction completes in 2 to 10 hours.

Parts of the raw material compounds represented by the general formula [II] are publicly known, but they can be svnthesized advantageously through the process below.

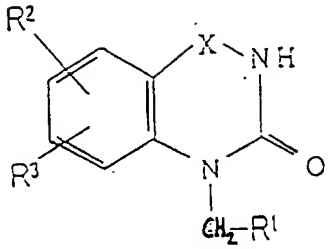


[XIX]

[wherein R, R^2, R^3, X and n are as described above].

Namely, they can be obtained by heating compounds represented by a general formula [XIX] with N, N'-carbonyldiimidazole at 80 to 160 °C in a solvent such as dimethylformamide or dioxane or without solvent.

1-b) Also, compounds of the general formula [I] can be obtained by reacting compounds represented by the general formula [IV]



[IV]

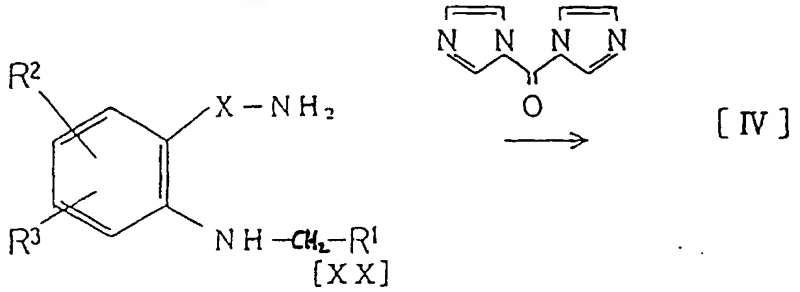
[wherein R^1, R^2, R^3, X, and n are as described above], with compounds represented by the general formula [V]

$$Z\text{-}(CH_2)n\text{-}COOR \qquad [V]$$

[wherein R, n and Z are as described above],
in the presence of a suitable base.

This reaction can be conducted advantageously in a solvent such as ethanol, dimethylformamide or dimethyl sulfoxide and in the presence of said alkali metal hydride, lower alkoxide, alkali metal hydroxide, alkali metal carbonate or organic base as a base. In this case, sodium hydride or potassium carbonate is preferable. At this time, adding of alkali metal iodide is advantageous in order to promote the reaction.

The raw material compounds represented by the general formula [IV] are publicly known in part, but they can be syntherized through the process below.



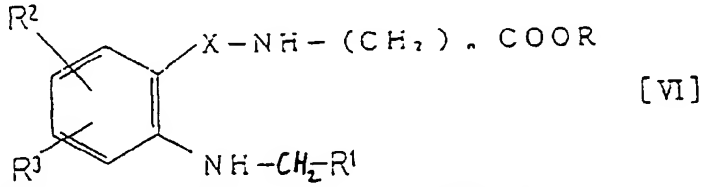
[IV]

[XX]

[wherein R^1, R^2, R^3 and X are as described above].

Namely, they can be obtained by heating compounds represented by a general formula [XX] with N,N'-carbonyldiimidazole at 80 to 150 °C in a solvent such as dimethylformamide or dioxane or without solvent.

1-c) Compounds of the general formula [I] can be obtained by heating compounds represented by a general formula [VI]



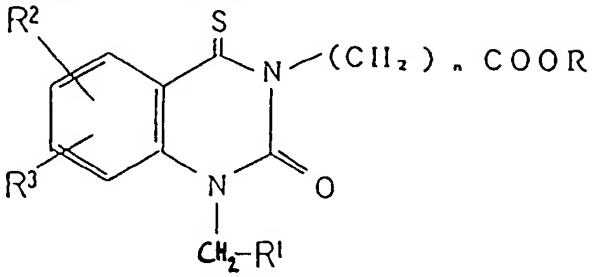
[VI]

[wherein R, R^1, R^2, R^3, X and n are as described above], with N,N'-carbonyldiimidazole at 80 to 150 °C in a solvent such as dimethylformamide or dioxane or without solvent. N,N'-carbonyldiimidazole is preferable to be used in amount of equimole or more. The reaction completes in 1 to 5 hours.

2) Compounds, wherein R is hydrogen in the general formula [I], can be obtained by hydrolyzing the ester type protecting group for carboxylic acid. This hydrolysis can be conducted in the presence of base or acid. Preferable bases are alkali metal hydroxides (e.g. sodium hydroxide or potassium hydroxide) and the hydrolysis is carried out within a temperature range from room temperature to the boiling point of the solvent. As the acids, organic acids such as, for example, formic acid, acetic acid, propionic acid or benzenesulfonic acid, inorganic acids such as, for example, hydrochloric acid, hydrobromic acid or sufuric acid, or their mixtures can be used. This reaction is usually performed under heating using an excess amount of acid.

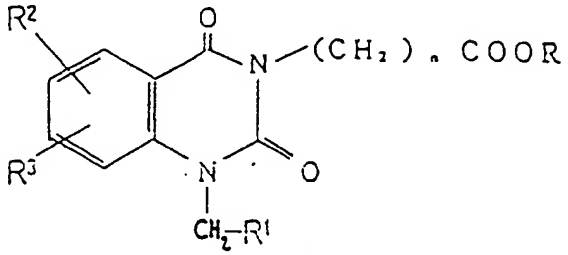
In both cases, as the reaction solvent, water, acetone, methanol, ethanol, propanol or dimethylformamide is used.

3) Compounds represented by the general formula [VIII]



[VIII]

[wherein R, R^1, R^2, R^3 and n are as described above],
can be obtained by reacting compounds represented by a general formula [IX]

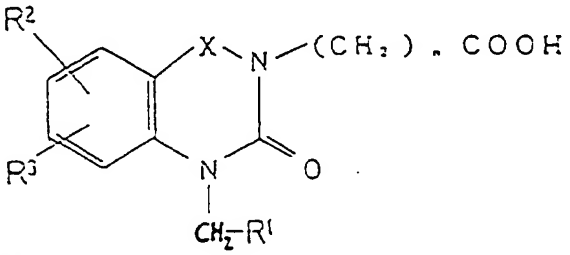


[IX]

[wherein R, R^1, R^2, R^3 and n are as described above],
which are obtainable by the methods under 1-a) to c) and 2) aforementioned, with a suitable sulfide. As the sulfides to be used for this reaction, for example, Lawesson's reagent or phosphorus pentasulfide can be mentioned.

This reaction is conducted usually under nonaqueous concitions and in a common solvent being inert to the reaction such as chloroform, methylene chloride, dioxane, carbon disulfide, benzene or toluene, using not less than equimol, preferably two to five times moles of said sulfide. The reaction temperature is within a range from room temperature to 120 °C and the reaction completes by continuing for 1 to 5 hours.

4) Moreover, compounds, R indicating a protecting group for carboxyl group in the general formula [I], can be obtained by reacting compounds represented by a general formula [X]



[X]

[wherein R^1, R^2, R^3, X and n are as described above],
with compounds represented by a general formula [XI]

R'-Z [XI]

[wherein R' indicates a protecting group for carboxyl group and Z is as described above],
in the presence of a suitable base. As the bases to be used for this reaction, alkali metals such as, for example, lithium or sodium, alkali metal hydrides such as, for example, sodium hydride, alkali metal hydroxides such as, for example, sodium hydroxide or potassium hydroxide, alkali metal carbonates such as, for example, sodium carbonate or potassium carbonate, alkali metal alkoxides such as, for example, sodium methoxide and organic bases such as, for example, triethylamine and pyridine can be mentioned. Usually, this reaction is conducted in a solvent being inert to the reaction such as acetone, dimethylformamide or chloroform within a range from room temperature to 120 °C and it completes in 30 minutes to 2 hours.

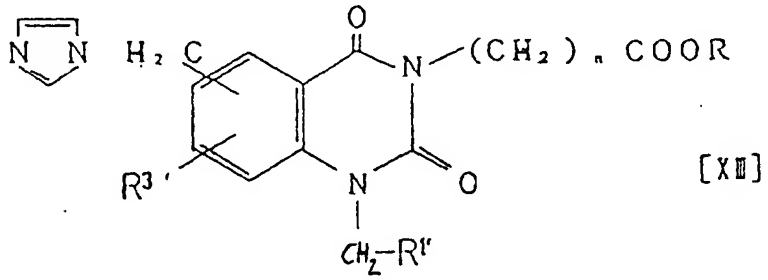
Compounds, wherein R indicates a protecting group for the carboxyl group in the general formula [I], can also be obtained by reacting reactive derivatives of compounds represented by the general formula [X] with compounds represented by a general formula [XII]

R'-OH [XII]

[wherein R' is as described above].

For example, they can be obtained by reacting reactive derivatives of [X], for example, acid halides, with lower alcohol such as methanol or ethanol, aralkyl alcohol such as, for example, benzyl alcohol, hydroxy lower alcohol such as, for example, ethylene glycol or methoxyethyl alcohol, in which hydroxyl group may be substituted, in an aprotic solvent such as, for example, chloroform, tetrahydrofuran or dimethylformamide or without solvent.

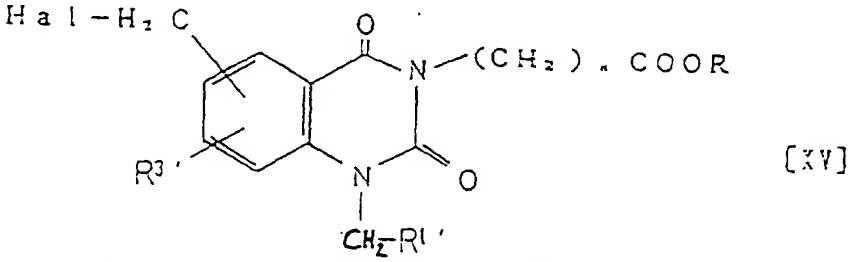
5) Compounds represented by a general formula [XIII]



[XIII]

[wherein $R^{1'}$, is phenyl group (this phenyl group may be substituted by one to three of lower alkyls, lower alkoxys, halogens, trifluoromethyls, carboxyethylenes or ethoxycarbonylethylenes), $R^{3'}$ is hydrogen, halogen or lower alkoxy group and R and n are as described above],

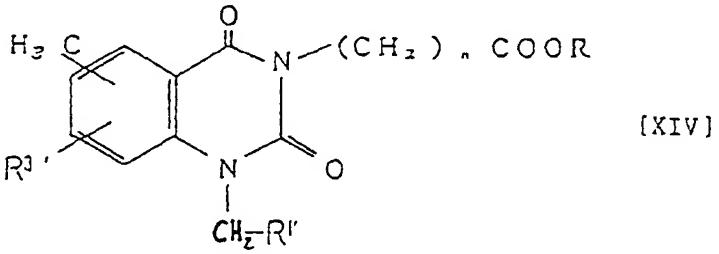
can be obtained by condensing imidazole with compounds represented by a general formula [XV]



[XV]

[wherein Hal is halogen and R, $R^{1'}$, $R^{3'}$ and n are as described above],

which are obtained by halogenation of compounds represented by general formula [XIV]



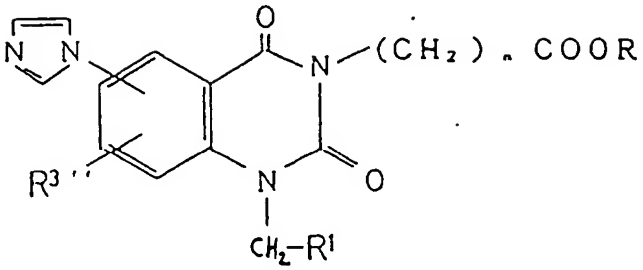
[XIV]

[wherein R, $R^{1'}$, $R^{3'}$ and n are as described above],

with halogenating agent such as chlorine, bromine or N-chlorosuccinimide.

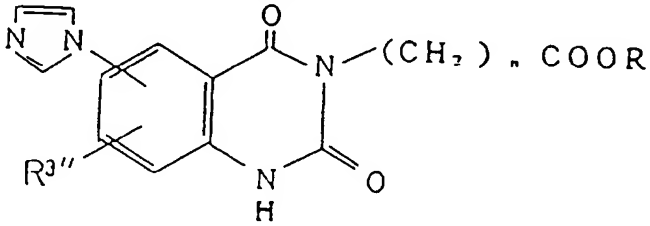
The halogenation can be usually conducted advantageously in a solvent such as carbon tetrachloride, acetic acid or chloroform, using peroxide such as benzoyl peroxide or under the irradiation of light. The reaction is made within temperature range from room temperature to the boiling point of the solvent and it completes in 2 to 6 hours. The condensation with imidazole can be achieved by heating at 80 to 120 °C in a solvent such as dioxane, dimethylformamide or dimethylacetamide in the presence of a suitable base. As the bases, alkali metal carbonates such as potassium carbonate or sodium carbonate, or imidazole itself are desirable.

6) Compounds represented by a general formula [XVI]



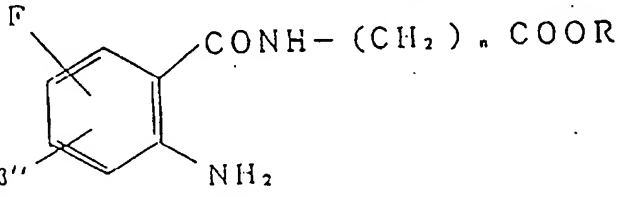
[XVI]

[wherein $R^{3''}$ is hydrogen, halogen, lower alkyl group, lower alkoxy group, aralkyl group or nitro group and R, R^1 and n are as described above],
can be obtained by reacting compounds represented by a general formula [XVIII]



[XVII]

[wherein R, $R^{3''}$ and n are as described above],
which are obtainable by heating compounds represented by a general formula [XVII]



[XVI]

[wherein R, $R^{3''}$ and n are as described above],
with equimole or more N,N^1-carbonyldiimidazole at 100 to 160 °C in dioxane or dimethylformamide or without solvent, with compounds represented by a general formula [III]

$$R^1\text{-}CH_2\text{-}Z \qquad [III]$$

[wherein R^1 and Z are as described above],
under similar conditions to 1-a).

Compounds represented by the general formula [XVII] can be obtained by condensing 4,5-difluoroisatoic anhydride with aminoalkanic acid or its ester (e.g. glycine, 2-aminopropionic acid or alanine, their ester derivatives and their salts).

This reaction is conducted within a temperature range from room temperature to 70 °C in ethanol, dioxane or mixtures of these solvents with water in the presence of a suitable base (e.g. potassium carbonate, sodium carbonate, triethylamine, piperidine or pyridine).

The compounds obtainable through the processes as above can be isolated and purified by publicly known separating and purifying means, for example, by solvent extraction, recrystallization or chromatography.

When salts of compounds represented by the general formula [I], which are pharmaceutically permissible, are further required, they can be obtained by reacting with base coexisting cation such as, for example, sodium hydroxide or potassium hydroxide, inorganic acid such as, for example, hydrochloric acid or sulfuric acid, or organic acid such as, for example, fumaric acid or oxalic acid according to usual methods. Best embodiment for putting the invention into practice.

The preparation examples and the examples of the invention will be described to illustrate the invention in more detail.

Referential example 1

Ethyl (2-amino-5-chlorobenzoyl)aminoacetate

Into a mixed liquor of 160 ml of dioxane with 40 ml of water were dissolved 10.5 g of glycine ethyl ester hydrochloride, and 11.9 g of 6-chloro-2H-3,1-benzoxazine-2,4(1H)-dione were added. To this were added dropwise 8.1 g of triethylamine at room temperature under stirring, and the mixture was stirred for 30 minutes. After stirring further for 1 hour, dioxane was distilled off and 100 ml of water were added. The deposits were collected by filtration, washed with water and dried. Then, these were recrystallized from carbon tetrachloride to obtain 11.0 g of title compound. m.p. 108 - 110 °C

Elemental analysis (%) as $C_{11}H_{13}ClN_2O_3$			
Calculated	C: 51.47	H: 5.10	N: 10.92
Observed	C: 51.27	H: 5.08	N: 10.88

Referential example 2

Ethyl 6-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazoline-acetate

Into 35 ml of dioxane were dissolved 27.6 g of compound of Referential example 1, and, after added 35 g of N,N'-carbonyldiimidazole, the mixture was heated to 150 °C. After distilled off dioxane, the reaction mixture was heated further for 20 minutes under stirring. After cooling, methanol was added and the crystals deposited were collected by filtration and dried. They were recrystallized from dioxane to obtain 28.6 g of title compound. m.p. 214.0 - 215.0 °C

Elemental analysis (%) as $C_{12}H_{11}ClN_2O_4$			
Calculated	C: 50.98	H: 3.92	N: 9.91
Observed	C: 50.68	H: 3.84	N: 9.88

Referential example 3

2-(4-Chlorophenylmethylamino)benzamide

In 400 ml of concentrated aqueous ammonia, 14.4 g of 1-(4-chlorophenylmethyl)-2H-3,1-benzoxazine-2,4(1H)-dione were heated to 100 °C and stirred for 3 hours. After cooling, the crystals were collected by filtration, washed with water and dried. They were recrystallized from ethanol to obtain 8.6 g of title compound. m.p. 138 - 139 °C

Referential example 4

1-(4-Chlorophenylmethyl)quinazoline-2,4-(1H,3H)-dione

In 10 ml of dioxane, 3.5 g of compound of Referential example 3 and 4.4 g of N,N'-carbonyldiimidazol were heated to 150 °C. After distilled off dioxane, the reaction mixture was heated further for 30 minutes under stirring. After cooling, it was permeated with methanol and the crystals deposited were collected by filtration and dried. They were recrystallized from dioxane to obtain 30 g of title compound. m.p. 217 - 218 °C

Elemental analysis (%) as $C_{15}H_{11}ClN_2O_2$			
Calculated	C: 62.83	H: 3.87	N: 9.77
Observed	C: 62.88	H: 3.70	N: 9.75

Referential example 5

Ethyl [2-[N-(2,4-dichlorophenyl)methyl]amino-5-methoxybenzoyl]aminoacetate

Into a mixed liquor of 150 ml of dioxane with 30 ml of water were dissolved 5.0 g of 1-(2,4-dichlorophenyl)methyl-6-methoxy-2H-3,1-benzoxazine-2,4(1H)-dione, and 2.4 g of glycine ethyl ester hydrochloride were added and further 1.9 g of triethylamine were added dropwise. The mixture was refluxed for 3 hours. After cooling, solvent was distilled

off, water was added, and the reaction mixture was extracted with ethyl acetate. It was dried and the solvent was distilled off to obtain 4.7 g of title compound as an oily product.

Referential example 6

Ethyl (2-amino-4,5-difluorobenzoyl)aminoacetate

Into a mixed liquor of 280 ml of dioxane with 70 ml of water were dissolved 19 g of glycine ethyl ester hydrochloride, and 21.7 g of 6,7-difluoro-2H-3,1-benzoxazine-2,4(1H)-dione were added and 14.7 g of triethylamine were added dropwise at room temperature under stirring. After stirring further for 30 minutes, the mixture was heated to 70 °C and stirred for 1,5 hours. Dioxane was distilled off, 150 ml of water were added, then the crystals deposited were collected by filtration, washed with water, and dried. They were recrystallized from ethyl acetate to obtain 20 g of title compound. m.p. 147 °C

Elemental analysis (%) as $C_{11}H_{12}F_2N_2O_3$			
Calculated	C: 51.16	H: 4.69	N: 10.85
Observed	C: 50.78	H: 4.31	N: 10.36

Example 1

Ethyl 6-chloro-1-(4-chlorophenyl)methyl-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetata

Into 30 ml of dimethylformamide were suspended 0.34 g of sodium hydride (60 %), and 2.00 g of 6-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetate were added. After stirring for 10 minutes at room temperature, 1.25 g of 2-chlorobenzyl chloride were added and the mixture was stirred for 20 minutes at room temperature and further for 1 hour at 70 °C. After cooling, the reaction mixture was poured into water and the deposits were collected by filtration. They were recrystallized from ethanol to obtain 0.78 g of title compound. m.p. 137 - 138 °C

Elemental analysis (%) as $C_{19}H_{16}Cl_2N_2O_4$			
Calculated	C: 56.03	H: 3.96	N: 6.88
Observed	C: 56.12	H: 3.88	N: 6.77

Example 2

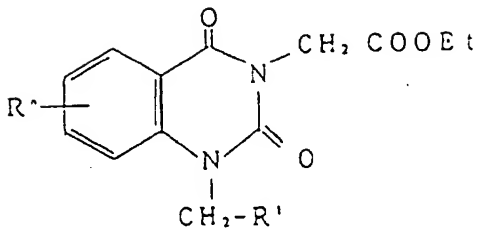
Ethyl 1-(4-bromo-2-fluorophenyl)methyl-6-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetate

Into 250 ml of dried dimethylformamide were dissolved 10 g of ethyl 6-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetate, and 4.86 g of potassium carbonate were added and 10.40 g of 4-bromo-2-fluorobenzyl bromide were added under stirring. After stirring for 1 hour at 60 °C, the reaction mixture was poured into 400 ml of ice water and the crystals were collected by filtration. They were recrystallized from ethanol to obtain 12.0 g of title compound. m.p. 145 - 146 °C

Elemental analysis (%) as $C_{19}H_{15}BrFN_2O_4$			
Calculated	C: 48.59	H: 3.22	N: 5.96
Observed	C: 48.54	H: 3.18	N: 5.96

Example 3 - 60

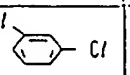
Following compounds were obtained through similar processes to Example 1 and 2.

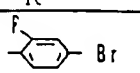
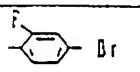
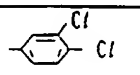
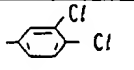
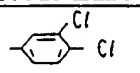
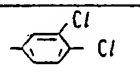
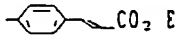


Example	R°	R'	m.p. (°C) (Recryst. solvent)
3	6-Cl		146-148 (EtOH)
4	6-Cl		130-132 (EtOH)
5	6-Cl		137-138 (EtOH)
6	6-Cl		161-162 (CH_3CN)
7	6-Cl		138-139 (EtOH)
8	6-Cl		174-175 (EtOH)
9	6-Cl		177-178 (CH_3CN)
10	6-Cl		174-175 (CH_3CN)
11	H		114-115 (EtOH)
12	6-F		134.5-135.5 (CH_3CN)
13	6-F		160-161 (CH_3CN)

Example	R^a	R^1	m.p. (°C) (Recryst. solvent)
14	6-Cl		153-154 (EtOH)
15	6-Cl		144-145 (CH_3CN)
16	6-Cl		134-136 (EtOH)
17	H		142-143 (EtOH)
18	6-Cl		149 (CH_3CN)
19	6-F		127-128 (EtOH)
20	7-Cl		167-168 (CH_3CN)
21	6,7-$(OCH_3)_2$		176-178 (CH_3CN)
22	6-Cl		142-143 (Cyclohexane)
23	6-Cl		165-166 (EtOH)
24	6-Cl		165-166.5 (CH_3CN)
25	7-Cl		180-181 (CH_3CN)
26	6-Cl		147-148 (EtOH)
27	6-CH_3		167 (EtOH)

Example	R^a	R^1	m.p. (°C) (Recryst. solvent)
28	6, 7-$(OCH_3)_2$		128-129 (CH_3CN)
29	6-Br		168 (CH_3CN)
30	6-Br		164-164.5 (CH_3CN)
31	6-CH_3		168 (EtOH)
32	H		138-139 (EtOH)
33	6-Cl		120-121 (EtOH)
34	6-Cl		154-155 (EtOH)
35	6-F		147 (EtOH)
36	5-Cl		161-162 (EtOH)
37	5-Cl		163-164 (EtOH)
38	6, 8-Cl_2		107-109 (EtOH)
39	6-Cl		141-142 (EtOH)
40	6, 7-$(OCH_3)_2$		152-153 (CH_3CN)
41	6-Et		140-141 (EtOH)

Example	R^a	R^1	m.p. (°C) (Recryst. solvent)
42	6-NO_2		155-156 (EtOH)
43	6-Et		125-126 (EtOH)
44	6,7-$(OCH_3)_2$		153-155 (EtOH)
45	6-F		161 (CH_3CN)
46	6-CH_3		156-158 (CH_3CN)
47	5-Cl		156 (EtOH)
48	7-Cl		155-156 (EtOH)
49	6-Br		147-148 (EtOH)
50	6- 		155-156 (EtOH)
51	6-$N(CH_3)_2$		143-144 (EtOH)
52	6-NO_2		138-138.5 (EtOH)
53	6- 		173-174 (CH_3CN)

Example	R"	R'	m.p. (°C) (Recryst. solvent)
54	6-N(CH$_3$)$_2$		146-147 (EtOH)
55	6-OCH$_3$		129-130 (EtOH)
56	6- 		144-145 (EtOH)
57	6-SCH$_3$		114-115 (EtOH)
58	6-OCH$_3$		130-131 (EtOH)
59	5-Cl		155-156 (EtOH)
60	6-Cl		155-157 (EtOH)

Example 61

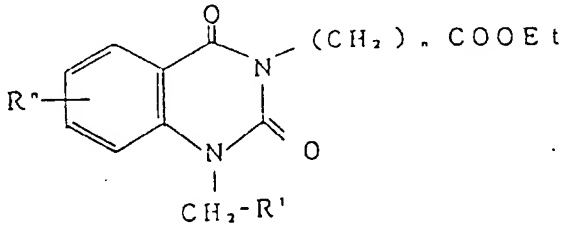
Ethyl 1-(4-clorophenyl)methyl-1,4-dihydro-2,4dioxo-3(2H)-quinazolineacetate

Into 20 ml of dried dimethylformamide were suspended 0.24 g of sodium hydride, and, after added 1.43 g of 1-(4-chlorophenyl)-methyl-3H-quinazoline-2,4-dione to this, the mixture was stirred for 15 minutes. Thereafter, 0.92 g of ethyl bromoacetate were further added dropwise and the mixture was stirred for 2 hours at room temperature. After cooling by allowing to stand, the reaction mixture was poured into 500 ml of water and the deposits were collected by filtration. They were recrystallized from ethanol to obtain 1.29 g of title compound. m.p. 138 - 139 °C

Elemental analysis (%) as $C_{19}H_{17}ClN_2O_4$			
Calculated	C: 61.21	H: 4.60	N: 7.52
Observed	C: 61.12	H: 4.45	N: 7.48

Example 62-65

Following compounds were obtained through similar process to Example 61.



Example	R^a	R^1	n	m.p. (°C) (Recryst. solvent)
62	H		2	98-100 (EtOH)
63	6-Cl		1	168-168.5 (EtOH)
64	H		2	117-118 (EtOH)
65	H		3	109-110 (EtOH)

Example 66

1-(4-Bromo-2-fluorophenyl)methyl-6-ch1oro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetic acid

Into 280 ml of concentrated hydrochloric acid and 140 ml of acetic acid were suspended 18.0 g of ethyl 1-(4-bromo-2-fluorophenyl)methyl-6-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetate, and, after added 1 ml of concentrated sulfuric acid, the mixture was refluxed for 3 hours, After cooling, the reaction liquor was poured into 600 ml of ice water and the deposits were collected by filtration. They were recrystallized from ethanol to obtain 15,0 g of title compound. m.p. 189 °C

Elemental analysis (%) as $C_{17}H_{11}BrClFN_2O_4$			
Calculated	C: 46.23	H: 2.51	N: 6.34
Observed	C: 46.28	H: 2.39	N: 6.30

Example 67

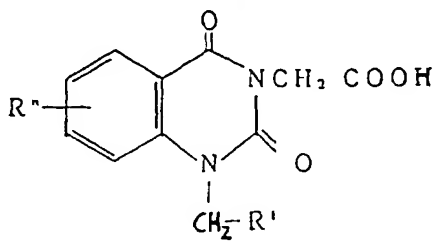
6-Chloro-1-(4-fluorophenyl)methyl-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetic acid

Into 50 ml of ethanol were dissolved 1.59 g of ethyl 6-chloro-1-(4-fluorophenyl)methyl-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetate, and after added 5 ml of aqueous solution containing 0.30 g of potassium hydroxide, the mixture was refluxed for 1 hour. After cooling by allowing to stand, ethanol was distilled off and the residue was dissolved by adding 30 ml of water, acidified with concentrated hydrochloric acid, and the deposits were collected by filtration. They were recrystallized from acetonitrile to obtain 0.75 g of title compound. m.p. 211 - 212 °C

Elemental analysis (%) as $C_{17}H_{12}ClFN_2O_4$			
Calculated	C: 56.28	H: 3.34	N: 7.72
Observed	C: 56.26	H: 3.29	N: 7.68

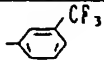
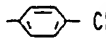
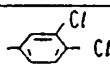
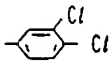
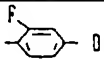
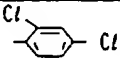
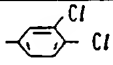
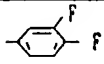
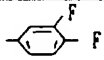
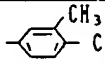
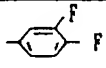
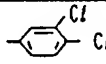
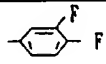
Example 68-150

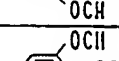
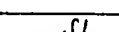
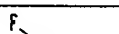
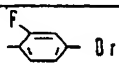
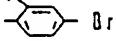
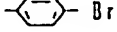
Following compounds were obtained through similar processes to Example 85 and 86.

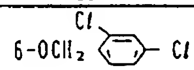
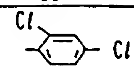
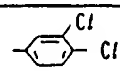
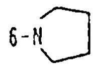
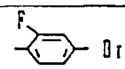
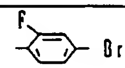
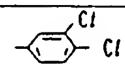
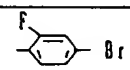
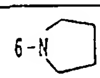
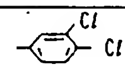
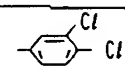
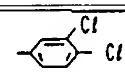
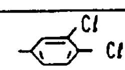


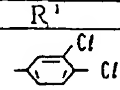
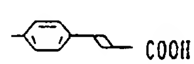
Example	R^n	R^1	m.p. (°C) (Recryst. solvent)
68	H		222-223 (EtOH)
69	6-Cl		204-205 (CH_3CN)
70	6-Cl		118-120 (CH_3CN)
71	6-Cl		>300 (DMF)
72	6-Cl		95-97 (EtOH)
73	6-Cl		257-258 (EtOH)
74	6-Cl		117-119 (CH_3CN)
75	6-Cl		225-226 (AcOH)
76	6-Cl		208-209 (AcOH)
77	6-OCH_3		238-239 (EtOH)
78	6-Cl		174 (EtOH)

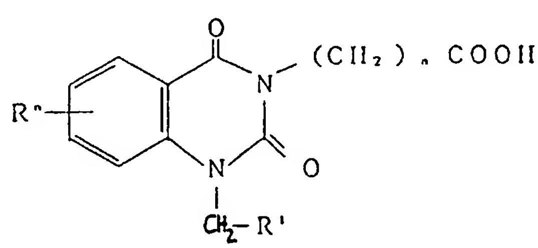
Example	R^n	R^1	m.p. (°C) (Recryst. solvent)
79	6-Cl		245-246 (EtOH)
80	6-Cl		291-292 (AcOH)
81	6-CH_3		232-233 (iPrOH)
82	H		201-202 (AcOH)
83	6-F		184-185 (CH_3CN)
84	6-F		206-207 (CH_3CN)
85	6-Cl		222-223 (CH_3CN)
86	H		182-185 (Benzene)
87	6-Cl		233-234 (EtOH)
88	6-F		190-191 (EtOH)
89	7-Cl		238-239 (EtOH)
90	6,7-$(OCH_3)_2$		247-248 (AcOH))
91	6-Cl		204-205 (CH_3CN)
92	6-Cl		216-217 (CH_3CN)
93	7-Cl		199-200 (CH_3CN)

Example	R^a	R^1	m.p. (°C) (Recryst. solvent)
94	6-Cl		173-174 (Benzene)
95	6-Cl		195-200 (Benzene)
96	6-CH_3		217-219 (EtOH)
97	6,7-$(OCH_3)_2$		197-198 (EtOH)
98	H		172-173 (EtOH)
99	6-Br		219-220 (Toluene)
100	6-Br		193-194 (Benzene)
101	6-CH_3		178 (CH_3CN)
102	H		171-172 (CH_3CN)
103	6-Cl		194-195 (Toluene)
104	6-F		168-170 (Toluene)
105	5-Cl		135-137 (CH_3CN)
106	5-Cl		200-201 (CH_3CN)

Example	R^n	R^1	m.p. (°C) (Recryst. solvent)
107	6-Cl		202-205 (CH_3CN)
108	6-NO_2		215-217 (EtOH)
109	6-Cl		268-269 (CH_3CN)
110	6,7-$(OCH_3)_2$		225-226 (CH_3CN)
111	6-Et		226-227 (Toluene)
112	6-Et		215-216 (Benzene)
113	6,7-$(OCH_3)_2$		233-235 (CH_3CN)
114	6-F		181-182 (EtOH)
115	6-CH_3		214-215 (EtOH)
116	7-Cl		202-203 (AcOEt)
117	5-Cl		191-192 (CH_3CN)
118	6-Br		204-204.5 (CH_3CN)

Example	R"	R'	m.p. (°C) (Recryst. solvent)
119			214-215 (AcOH)
120	6-N(CH₃)₂		197-198 (i-PrOH)
121			248-249 (EtOH)
122	6-N(CH₃)₂		211-212 (EtOH)
130	6-N(CH₃)₂		204-205 (CH₃CN)
140	6-Cl		226-228 (CH₃CN)
141	6-OCH₃		218-219 (EtOH)
142			189-190 (EtOH)
143	6-SCH₃		208-210 (EtOH)
144	6-OCH₃		253-255 (EtOH)
145	6,8-Cl₂		149-150 (Chloroform-hexane)

Example	R"	R'	m.p. (°C) (Recryst. solvent)
146	5-Cl		127-128 (Benzene)
147	6-Cl		>300 (Dioxane-hexane)



Example	R"	A	R'	n	m.p. (°C) (Recryst. solvent)
148	H	$-CH_2-$		2	197.5-198 (EtOH)
149	H	$-CH_2-$		2	192-193 (EtOH)
150	H	$-CH_2-$		3	170 (EtOH)

Example 151

Hydroxyethyl 6-chloro-1-(2,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetate

Into 10 ml of dried dimethylformamide were suspended 60 mg of sodium hydride (60 %), and, to this was added dropwise a solution dissolved 500 mg of 6-chloro-1-(2,4-dichlorophenyl)-methyl-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetic acid into 3 ml of dried dimethylformamide under stirring. After stirring the mixture for 30 minutes at room temperature, 160 mg of ethylene bromohydrin were added and the mixture was stirred for 4 hours at 110 °C. After cooling by allowing to stand, the reaction mixture was poured into 200 ml of water and acidified with hydrochloric acid, which was extracted with ethyl acetate. After dried over anhydrous magnesium sulfate, solvent was distilled off and the residue was recrystallized from ethanol to obtain 300 mg of title compound. m.p. 167 - 168 °C

Elemental analysis (%) as $C_{19}H_{15}Cl_3N_2O_5$			
Calculated	C: 49.86	H: 3.30	N: 6.12
Observed	C: 49.88	H: 3.21	N: 6.16

Example 152

Following compound was synthesized through similar process to Example 151.

Pivaloyloxymethyl 6-chloro-1-(3,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetate. m.p. 125 - 126 °C (EtOH)

Example 153

Ethyl 1-(2,4-dichlorophenyl)methyl-1,4-dihydro-2-oxo-4-thioxo-3(2H)-quinazolineacetate

Into 100 ml of toluene were dissolved 3.80 g of ethyl 1-(2,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetate, and 5.70 g of Lawesson's reagent were added. After refluxed for 7 hours and 30 minutes, 1.90 g of Lawesson's reagent were further added and, after refluxed for 5 hours, solvent was distilled off. To the residue were added 10 ml of ethanol for washing, then it was further recrystallized from ethanol to obtain 2.80 g of title compound. m.p. 138 - 139 °C

Elemental analysis as $C_{19}H_{16}Cl_2N_2O_3S$			
Calculated	C: 53.91	H: 3.81	N: 6.62
Observed	C: 53.98	H: 3.76	N: 6.61

Example 154-156

Following compounds were synthesized through similar process to Example 153.

Example 154

Ethyl 1-(4-bromo-2-fluorophenyl)methyl-1,4-dihydro-2-oxo-4-thioxo-3(2H)-quinazolineacetate. m.p. 109 - 110 °C (EtOH)

Example 155

Ethyl 1-(4-bromo-2-fluorophenyl)methyl-6-chloro-1,4-dihydro-2-oxo-4-thioxo-3(2H)-quinazolineacetate. m.p. 89 - 90 °C (EtOH)

Example 156

Ethyl 1-(3,4-dichlorophenyl)methyl-1,4-dihydro-6-methyl-2-oxo-4-thioxo-3(2H)-quinazolineacetate. m.p. 175.5 - 177 °C (EtOH)

Example 157

Ethyl 1-(3,4-dichlorophenyl)methyl-1,4-dihydro-2-oxo-4-thioxo-3(2H)-quinazolineacetate. m.p. 128 - 129 °C (EtOH)

Example 158

1-(2,4-Dichlorophenyl)methyl-1,4-dihydro-2-oxo-4-thioxo-3(2H)-quinazolineacetic acid

Into 10 ml of acetic acid were dissolved 500 mg of ethyl 1-(2,4-dichlorophenyl)methyl-1,4-dihydro-2-oxo-4-thioxo-3(2H)-quinazolineacetate, and, after added 3 ml of concentrated hydrochloric acid and then 0.5 ml of concentrated sulfuric acid, the mixture was refluxed for 1 hour. After cooling by allowing to stand, the reaction mixture was poured into 200 ml of water and the deposits were collected by filtration. They were recrystallized from acetic acid to obtain 300 mg of title compound. m.p. 220 - 221 °C

Elemental analysis as $C_{17}H_{12}Cl_2N_2O_3S$			
Calculated	C: 51.66	H: 3.06	N: 7.09
Observed	C: 51.90	H: 3.05	N: 7.02

Example 159-161

Following compounds were synthesized through similar process to Example 158.

Example 159

1-(4-Bromo-2-fluorophenyl)methyl-1,4-dihydro-2-oxo-4-thioxo-3(2H)-quinazolineacetic acid. m.p. 269 - 270.5 °C (EtOH)

Example 160

1-(4-Bromo-2-fluorophenyl)methyl-6-chloro-1,4-dihydro-2-oxo-4-thioxo-3(2H)-quinazolineacetic acid. m.p. 249.5 - 250.5 °C (AcOEt)

Example 161

1-(3,4-Dichlorophenyl)methyl-1,4-dihydro-2-oxo-4-thioxo-3(2H)-quinazolineacetic acid. m.p. 237 - 238 °C (CH_3CN)

Example 162

Ethyl 1-(2,4-dichlorophenyl)methyl-6-methoxy-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetate

Into 10 ml of dioxane were dissolved 5.2 g of ethyl (2-((2,4-dichlorophenyl)methyl)amino-5-methoxybenzoyl)aminoacetate and 6.2 g of N,N'-carbonyldiimidazole, and the solution was heated to 140 to 150 °C. After distilled off dioxane, the mixture was further heated for 15 minutes at 140 °C. After cooling, ethanol was added and the crystalline substances were collected by filtration. They were recrystallized from ethanol to obtain 2.8 g of title compound. m.p. 167 - 168 °C

Elemental analysis (%) as $C_{20}H_{18}Cl_2N_2O_5$			
Calculated	C: 54.94	H: 4.15	N: 6.41
Observed	C: 54.93	H: 4.11	N: 6.34

Example 163

Ethyl 1-(3,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-6-imidazolylmethyl-3(2H)-quinazolineacetate

In 30 ml of carbon tetrachloride were refluxed 3.5 g of ethyl 1-(3,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-6-methyl-3(2H)-quinazolineacetate, 1.66 g of N-bromosuccinimide and calalytic amount of benzoyl peroxide for 2 hours.

The insolubles were filtered off and the filtrate was concentrated. Ether was added to the residue for crystallization and the crystals thus obtained were recrystallized from acetonitrile to obtain 2.0 g of ethyl 6-bromomethyl-1-(3,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-3(2H)-quinazolineacetate. m.p. 128 - 129 °C

In 30 ml of dimethylformamide were stirred 1.90 g of above bromo compound, 0.28 g of imidazole and 0.53 g of potassium carbonate for 1.5 hours at 100 °C. After cooling by allowing stand, the reaction mixture was poured into 500 ml of water and the crystals deposited were collected by filtration. They were purified by means of silica gel column chromatography (developing solvent, chloroform:methanol=10:1) and recrystallized from acetonitrile to obtain 0.33 g of title compound. m.p. 201 - 202 °C

Elemental analysis (%) as $C_{23}H_{20}Cl_2N_4O_4$			
Calculated	C: 56.68	H: 4.14	N: 11.50
Observed	C: 56.57	H: 4.02	N: 11.26

Example 164

1-(3,4-Dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-6-imidazolylmethyl-3(2H)-quinazolineacetic acid

In 1.6 ml of IN aqueous solution of sodium hydroxide and 20 ml of ethanol were refluxed 0.71 g of ethyl 1-(3,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-6-imidazolylmethyl-3(2H)-quinazolineacetate for 1 hour. Ethanol was distilled off and the reaction mixture was neutralized with 3N hydrochloric acid. The crystals deposited were collected by filtration, washed with water and dried. They were recrystallized from acetic acid to obtain 0.50 g of title compound. m.p. 243 - 244 °C

Elemental analysis (%) as $C_{21}H_{16}Cl_2N_4O_4 \cdot H_2O$			
Calculated	C: 52.84	H: 3.80	N: 11.74
Observed	C: 52.55	H: 3.45	N: 11.45

Example 165

a) Ethyl 1,4-dihydro-2,4-dioxo-6-fluoro-7-imidazolyl-3(2H)-quinazolineacetate

A mixture of 20.0 g of ethyl (2-amino-4,5-difluorobenzoyl)-aminoacetate, 25.1 g of N,N'-carbonyldiimidazole and 35 ml of dioxane was heated to 150 °C and, after distilled off dioxane, the mixture was heated for 1 hour. After cooling by allowing to stand, the crystals obtained were washed with methanol and recrystallized from dimethylformamide to obtain 13.8 g of title compound. m.p. 276 - 278 °C

Elemental analysis (%) as $C_{15}H_{13}FN_4O_4$			
Calculated	C: 54.22	H; 3.94	N: 16.86
Observed	C: 54.03	H: 3.98	N: 16.74

b) Ethyl 1-(2,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-6-fluoro-7-imidazolyl-3(2H)-quinazolineacetate

Into 50 ml of dimethylformamide were dissolved 2.33 g of ethyl 1,4-dihydro-2,4-dioxo-6-fluoro-7-imidazolyl-3(2H)-quinazolineacetate, and, after added 0.97 g of potassium carbonate and 1.51 g of 2,4-dichlorobenzyl chloride, the mixture was stirred for 5 hours at 100 °C. After cooling by allowing to stand, the reaction mixture was poured into 500 ml of water and the deposits were collected by filtration. They were recrystallized from ethanol to obtain 2.25 g of title compound. m.p. 192 - 193 °C

Elemental analysis (%) as $C_{22}H_{17}Cl_2FN_4O_4$			
Calculated	C: 53.78	H: 3.49	N: 11.40
Observed	C: 53.62	H: 3.54	N; 11.30

Example 166-167

Following compounds were synthesized through similar process to Example 165.

Example 166

Ethyl 1,4-dihydro-2,4-dioxo-6-fluoro-7-imidazolyl-1-((4-trifluoromethyl)phenyl)methyl-3(2H)-quinazolineacetate. m.p. 132 - 133 °C (Et_2O)

Example 167

Ethyl 1-(3,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-6-fluoro-7-imidazolyl-3(2H)-quinazolineacetate. m.p. 129 - 130 °C (EtOH)

Example 168

1-(2,4-Dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-6-fluoro-7-imidazolyl-3(2H)-quinazolineacetic acid

Into 50 ml of ethanol were dissolved 2.0 g of ethyl 1-(2,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-6-fluoro-7-imidazolyl-3(2H)-quinazolineacetate, and, after added 4.5 ml of IN aqueous solution of sodium hydroxide, the mixture was refluxed for 1.5 hours. Ethanol was distilled off, water was added, pH was made to be 5 with 3N hydrochloric acid, and the deposits were collected by filtration. They were recrystallized from dioxane to obtain 930 mg of title compound. m.p. 188 - 189 °C

Elemental analysis (%) as $C_{20}H_{13}Cl_2FN_4O_4$

Calculated	C: 51.85	H: 2.83	N; 12.10
Observed	C: 51.91	H: 2.91	N: 11.94

Example 169-170

Following compounds were synthesized through similar process to Example 168.

Example 169

1,4-Dihydro-2,4-dioxo-6-fluoro-7-imidazolyl-1-((4-trifluoromethyl)phenyl)methyl-3(2H)-quinazolineacetic acid. m. p. 245 - 246 °C (dioxane)

Example 170

1-(3,4-Dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-6-fluoro-7-imidazolyl-3(2H)-quinazolineacetic acid. m.p. 251 - 253 °C (dioxane)

Utilizability in the industry

The novel quinazoline-3-alkanoic acid derivatives and their salts according to the invention have conspicuous hindering activity on aldose reductase and are useful drugs for the therapy and the prevention of complication of diabetes mellitus. Moreover, the compounds of the invention have excellent inhibitory effect on platelet aggregation and are also useful for the therapy of disorders of cerebral circulatory system, disease of arterial system, thrombosis, cardiac disease, ischemic fit and vascular disorders accompanied with diabetes mellitus.

Experimental example 1

<Inhibitory effect on aldose reductase>

Enzyme aldose reductase was partially purified from lens of rat and the inhibitory effect of the inventive compounds was determined using the method of Hyman et al (Hyman et al; J. Biol. Chem. 240, 877 (1965)). The IC_{50} value (drug concentration for inhibiting 50 % of enzyme activity) of the inventive compounds was 10^{-7} to 10^{-9}M showing excellent inhibitory effect on aldose reductase.

Experimental example 2

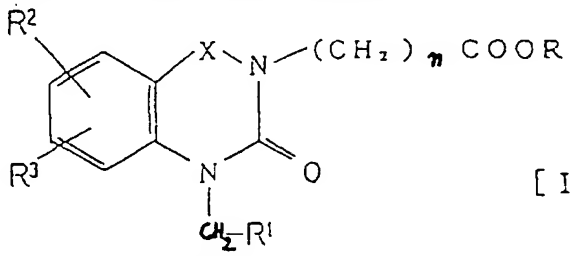
<Inhibitory effect on platelet aggregation>

Using citric acid-excess platelet plasma of rabbit, the aggregation caused by arachidonic acid was measured with aggregometer. The IC_{50} value (drug concentration for inhibiting 50 % of platelet aggregation) was 10^{-5} to 10^{-7}M showing excellent inhibitory effect on platelet aggregation.

Claims

Claims for the following Contracting States : BE, CH, LI, DE, FR, GB, IT, NL, SE

1. Quinazoline-3-alkanoic acid derivatives represented by the general formula (I)

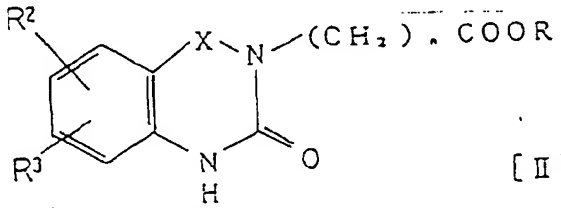


[I]

wherein R is hydrogen or a protecting group for the carboxyl group, R^1 is a phenyl group which may be substituted by one to three of lower alkyl group having 1 to 6 carbon atoms, lower alkoxy group having 1 to 3 carbon atoms, halogen, trifluoromethyl group, carboxyethylene group or ethoxycarbonylethylene group, R^2 and R^3 which are identical or different from each other, each represents hydrogen, halogen, lower alkyl group having 1 to 6 carbon atoms, lower alkoxy group having 1 to 3 carbon atoms, aralkyl group, nitro group, imidazolyl group, imidazolylmethyl group or

(R^4 and R^5 which are identical or different from each other, each represents hydrogen or lower alkyl group having 1 to 6 carbon atoms, or are connected with each other to form a five- or six-membered heterocyclic group which may contain other hetero atoms), X is a carbonyl or thiocarbonyl group, and n indicates an integer of 1 to 3, or their salts and the compounds: Ethyl 6-(2,4-dichlorobenzyloxy)-1-(2,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-3(2H) quinazoline acetate and 6-(2,4-dichlorobenzyloxy)-1-(2,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-3(2H) quinazoline acetic acid or their salts.

2. A process for preparing the quinazoline-3-alkanoic acid derivatives or their salts according to claim 1, **characterized in that** (a) compounds represented by the general formula (II)

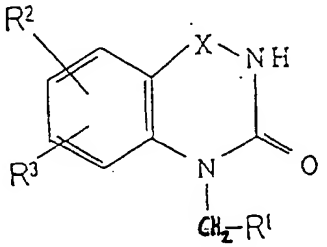


[II]

wherein R, R^2, R^3, X and n are as defined in claim 1, or their salts are reacted with compounds represented by the general formula (III)

$$R^1\text{-}CH_2\text{-}Z \qquad [III]$$

wherein Z is an eliminating group and R^1 is as defined in claim 1, or (b) compounds represented by the general formula (IV)

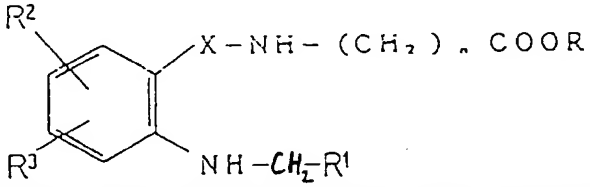


[IV]

wherein R^1, R^2, R^3 and X are as defined in claim 1, or their salts are reacted with compounds represented by the general formula (V)

$$Z\text{-}(CH_2)n\text{-}COOR \qquad [V]$$

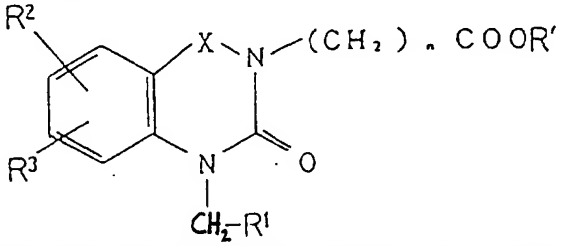
wherein Z is an eliminating group and Rand n are as defined in claim 1, or (c) compounds represented by the general formula (VI)



[VI]

wherein R, R^1, R^2, R^4, X and n are as defined in claim 1, or their salts are reacted with N,N'-carbonyldiimidazole.

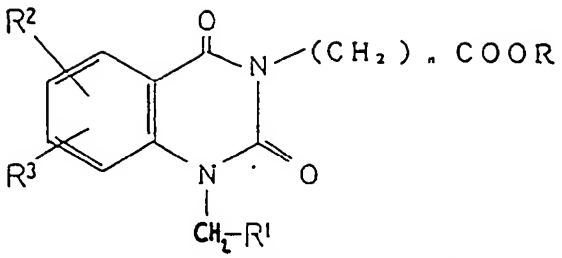
3. A process for preparing the quinazoline-3-alkanoic acid derivatives or their salts according to claim 1, wherein R is a hydrogen atom, **characterized in that** compounds represented by the general formula (VII)



[VII]

wherein R' is a protecting group for the carboxyl group and R^1, R^2, R^3, X and n are as defined in claim 1, are hydrolyzed.

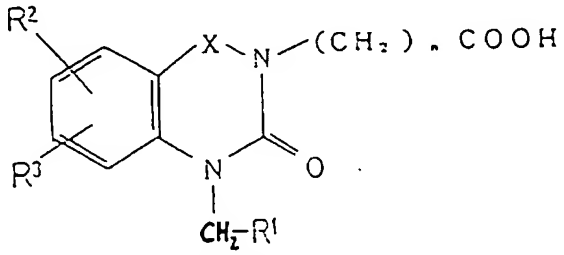
4. A process for preparing the quinazoline-3-alkanoic acid derivatives or their salts according to claim 1, wherein X is a thiocarbonyl group, **characterized in that** compounds represented by the general formula (IX)



[IX]

wherein R, R^1, R^2, R^3 and n are as defined in claim 1, are reacted with sulfide.

5. A process for preparing the quinazoline-3-alkanoic acid derivatives or their salts according to claim 1, wherein R is a protecting group for the carboxyl group, **characterized in that** compounds represented by the general formula (X)



[X]

wherein R^1, R^2, R^3, X and n are as defined in claim 1, are reacted with compounds represented by the general formula (XI)

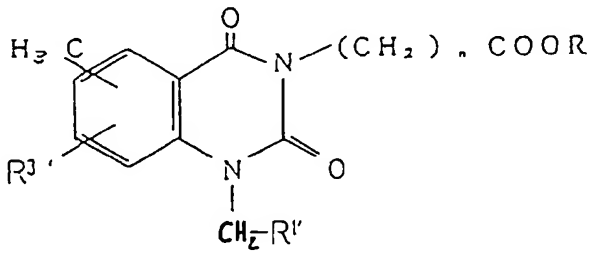
R'-Z [XI]

wherein R' is a protecting group for the carboxyl group and Z is an eliminating group, in the presence of a suitable base, or, after produced reactive derivatives of carboxylic acid once, then they are reacted with compounds represented by the general formula (XII)

R'-OH [XII]

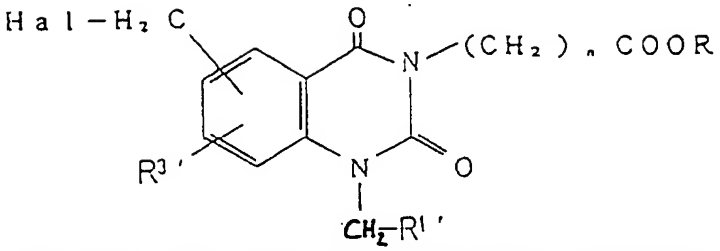
wherein R' is as described above.

6. A process for preparing the quinazoline-3-alkanoic acid derivatives or their salts according to claim 1, wherein R^2 is an imidazolylmethyl group, R^3 is hydrogen, halogen or lower alkoxy group having 1 to 3 carbon atoms and X is a carbonyl group, **characterized in that** with quinazoline-3-alkanoic acid derivatives represented by the general formula (XIV)



[XIV]

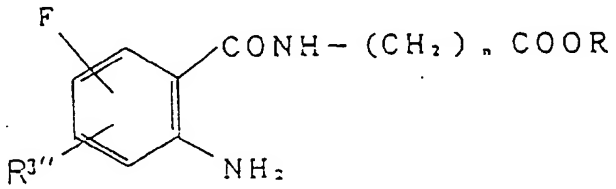
wherein $R^{1'}$ is a phenyl group (this phenyl group may be substituted by one to three of lower alkyl group having 1 to 6 carbon atoms, lower alkoxy group having 1 to 3 carbon atoms, halogen, trifluoromethyl group, carboxyethylene group or ethoxycarbonylethylene group), $R^{3'}$ is hydrogen, halogen or lower alkoxy group having 1 to 3 carbon atoms, and R and n are as defined in claim 1,
a halogenating agent is reacted to obtain compounds represented by the general formula (XV)



[XV]

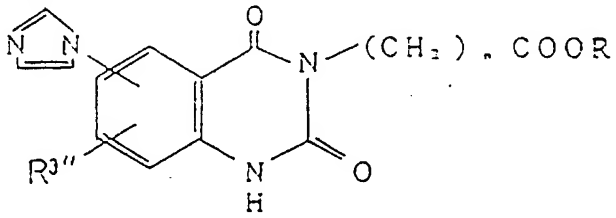
wherein Hal is halogen and R, $R^{1'}$, $R^{3'}$ and n are as described above, and then they are reacted with imidazole.

7. A process for preparing the quinazoline-3-alkanoic acid derivatives or their salts according to claim 1, wherein R^2 is an imidazolyl group, R^3 is hydrogen, halogen, lower alkyl group having 1 to 6 carbon atoms, lower alkoxy group having 1 to 3 carbon atoms, aralkyl group or nitro group, and X is a carbonyl group, **characterized in that** compounds represented by the general formula (XVII)



[XVII]

wherein $R^{3''}$ is hydrogen, halogen, lower alkyl group having 1 to 6 carbon atoms, lower alkoxy group having 1 to 3 carbon atoms, aralkyl group or nitro group and R and n are as defined in claim 1, are treated with N,N'-carbonyldiimidazole to obtain compounds represented by the general formula (XVIII)



[XVIII]

wherein R, $R^{3''}$ and n are as described above,
and then they are reacted with compounds represented by the general formula (III)

$$R^1\text{-}CH_2\text{-}Z \qquad [III]$$

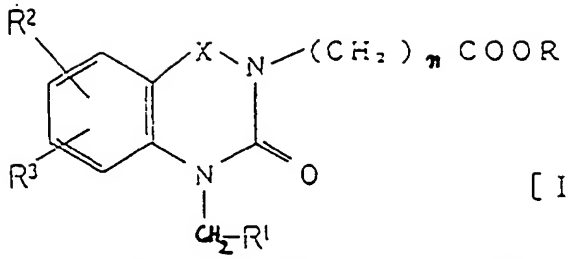
wherein Z is an eliminating group and R^1 is as defined in claim 1.

8. An inhibitor of platelet aggregation consisting of at least one kind of quinazoline-3-alkanoic acid derivatives represented by the general formula (I) or their salts, as defined in claim 1 as effective ingredient(s).

9. An inhibitory agent on aldose reductase consisting of at least one kind of quinazoline-3-alkanoic acid derivatives represented by the general formula (I) or their salts as defined in claim 1 as effective ingredient(s).

Claims for the following Contracting State : ES

1. A process for preparing quinazoline-3-alkanoic acid derivatives or their salts represented by the general formula (I)

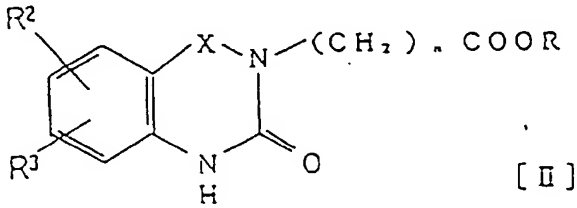


[I]

wherein R is hydrogen or a protecting group for the carboxyl group, R^1 is a phenyl group which may be substituted by one to three of lower alkyl group having 1 to 6 carbon atoms, lower alkoxy group having 1 to 3 carbon atoms. halogen, trifluoromethyl group, carboxyethylene group or ethoxycarbonylethylene group, R^2 and R^3 which are identical or different from each other, each represents hydrogen, halogen, lower alkyl group having 1 to 6 carbon atoms, lower alkoxy group having 1 to 3 carbon atoms, aralkyl group, nitro group, imidazolyl group, imidazolylmethyl group or

(R^4 and R^5 which are identical or different from each other, each represents hydrogen or lower alkyl group having 1 to 6 carbon atoms, or are connected with each other to form a five- or six-membered heterocyclic group which may contain other hetero atoms), X is a carbonyl or thiocarbonyl group, and n indicates an integer of 1 to 3, and for preparing the compounds:

Ethyl 6-(2,4-dichlorobenzyloxy)-1-(2,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-3(2H)quinazoline acetate and 6-(2,4-dichlorobenzyloxy)-1-(2,4-dichlorophenyl)methyl-1,4-dihydro-2,4-dioxo-3(2H)quinazoline acetic acid, **characterized in that** (a) compounds represented by the general formula (II)

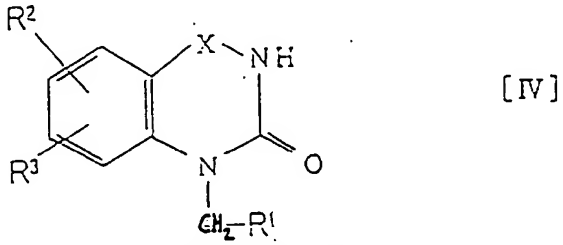


[II]

wherein R, R^2, R^3, X and n are as defined above, or their salts are reacted with compounds represented by the general formula (III)

$$R^1\text{-}CH_2\text{-}Z \qquad [III]$$

wherein Z is an eliminating group and R^1 is as defined above, or (b) compounds represented by the general formula (IV)

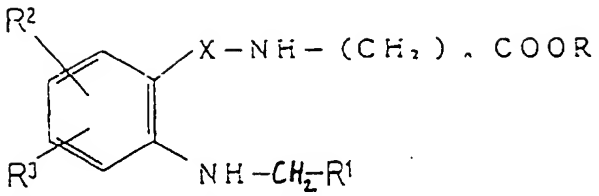


[IV]

wherein R^1, R^2, R^3 and X are as defined above, or their salts are reacted with compounds represented by the general formula (V)

$$Z\text{-}(CH_2)n\text{-}COOR \qquad [V]$$

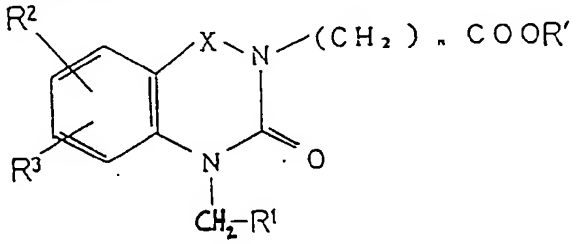
wherein Z is an eliminating group and R and n are as defined above, or (c) compounds represented by the general formula (VI)



[VI]

wherein R, R^1, R^2, R^4, X and n are as defined above, or their salts are reacted with N,N'-carbonyldiimidazole.

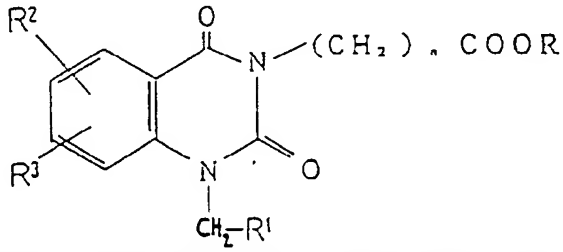
2. A process for preparing the quinazoline-3-alkanoic acid derivatives or their salts as defined in claim 1, wherein R is a hydrogen atom, **characterized in that** compounds represented by the general formula (VII)



[VII]

wherein R' is a protecting group for the carboxyl group and R^1, R^2, R^3, X and n are as defined in claim 1, are hydrolyzed.

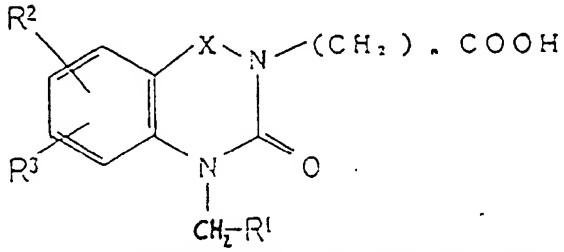
3. A process for preparing the quinazoline-3-alkanoic acid derivatives or their salts as defined in claim 1, wherein X is a thiocarbonyl group, **characterized in that** compounds represented by the general formula (IX)



[IX]

wherein R, R^1, R^2, R^3 and n are as defined in claim 1, are reacted with sulfide.

4. A process for preparing the quinazoline-3-alkanoic acid derivatives or their salts as defined in claim 1, wherein R is a protecting group for the carboxyl group, **characterized in that** compounds represented by the general formula (X)



[X]

wherein R^1, R^2, R^3, X and n are as defined in claim 1, are reacted with compounds represented by the general formula (XI)

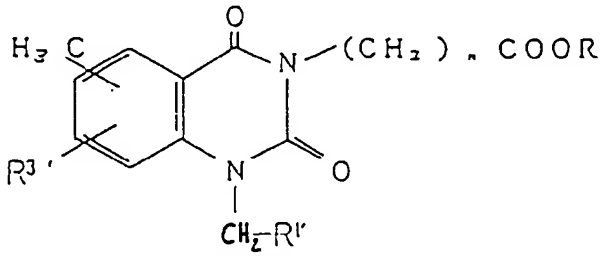
R'-Z [XI]

wherein R' is a protecting group for the carboxyl group and Z is an eliminating group, in the presence of a suitable base, or, after produced reactive derivatives of carboxylic acid once, then they are reacted with compounds represented by the general formula (XII)

R'-OH [XII]

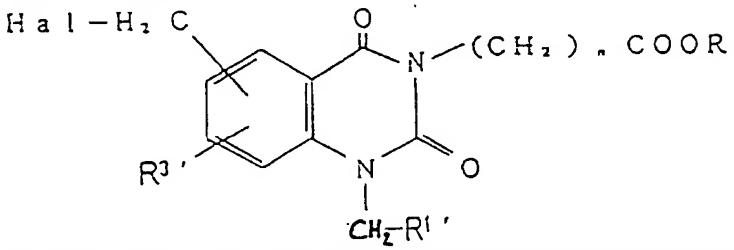
wherein R' is as described above.

5. A process for preparing the quinazoline-3-alkanoic acid derivatives or their salts as defined in claim 1, wherein R^2 is an imidazolylmethyl group, R^3 is hydrogen, halogen or lower alkoxy group having 1 to 3 carbon atoms and X is a carbonyl group, **characterized in that** with quinazoline-3-alkanoic acid derivatives represented by the general formula (XIV)



[XIV]

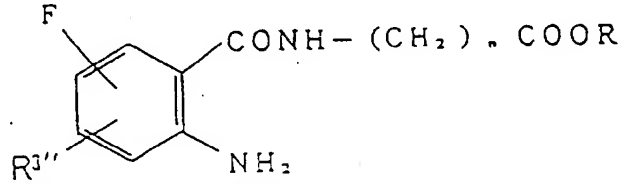
wherein $R^{1'}$ is a phenyl group (this phenyl group may be substituted by one to three of lower alkyl group having 1 to 6 carbon atoms, lower alkoxy group having 1 to 3 carbon atoms, halogen, trifluoromethyl group, carboxyethylene group or ethoxycarbonylethylene group), $R^{3'}$ is hydrogen, halogen or lower alkoxy group having 1 to 3 carbon atoms, and R and n are as defined in claim 1,
a halogenating agent is reacted to obtain compounds represented by the general formula (XV)



[XV]

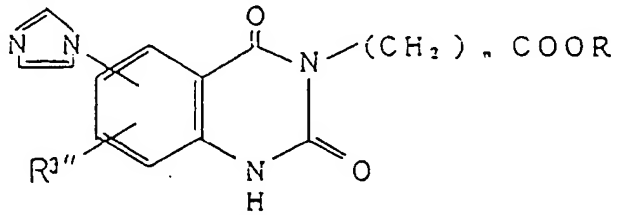
wherein Hal is halogen and R, $R^{1'}$, $R^{3'}$ and n are as described above, and then they are reacted with imidazole.

6. A process for preparing the quinazoline-3-alkanoic acid derivatives or their salts as defined in claim 1, wherein R^2 is an imidazolyl group, R^3 is hydrogen, halogen, lower alkyl group having 1 to 6 carbon atoms, lower alkoxy group having 1 to 3 carbon atoms, aralkyl group or nitro group, and X is a carbonyl group, **characterized in that** compounds represented by the general formula (XVII)



[XVII]

wherein $R^{3''}$ is hydrogen, halogen, lower alkyl group having 1 to 6 carbon atoms, lower alkoxy group having 1 to 3 carbon atoms, aralkyl group or nitro group and R and n are as defined in claim 1, are treated with N,N'-carbonyldiimidazole to obtain compounds represented by the general formula (XVIII)



[XVIII]

wherein R, $R^{3''}$ and n are as described above,
and then they are reacted with compounds represented by the general formula (III)

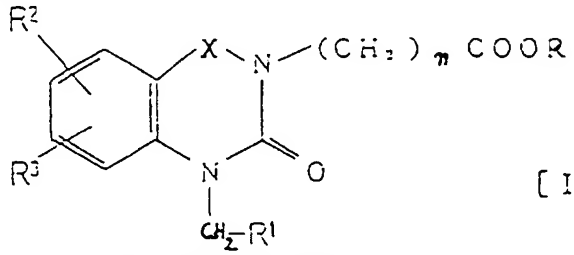
$$R^1\text{-}CH_2\text{-}Z \qquad [III]$$

wherein Z is an eliminating group and R^1 is as defined in claim 1.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, LI, DE, FR, GB, IT, NL, SE

1. Chinazolin-3-alkancarbonsäurederivate der allgemeinen Formel (I)

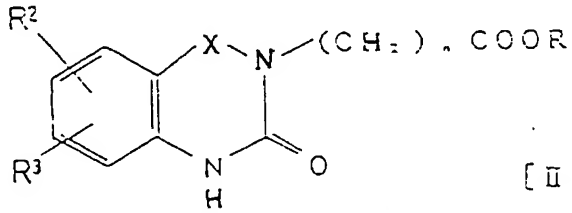


[I]

worin R Wasserstoff oder eine Schutzgruppe für die Carboxylgruppe ist, R^1 eine Phenylgruppe ist, welche durch eine bis drei aus einer Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen, Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, Halogen, Trifluormethylgruppe, Carboxyethylengruppe oder Ethoxycarbonylethylengruppe substituiert sein kann, R^2 und R^3, welche gleich oder voneinander verschieden sind, jeweils Wasserstoff, Halogen, eine Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen, Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, Aralkylgruppe, Nitrogruppe, Imidazolylgruppe, Imidazolylmethylgruppe oder

(worin R^4 und R^5, welche gleich oder voneinander verschieden sind, jeweils Wasserstoff oder eine Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeuten oder miteinander verbunden sind zur Bildung einer 5- oder 6-gliedrigen heterocyclischen Gruppe, welche weitere Heteroatome enthalten kann) bedeuten, X eine Carbonyl- oder Thiocarbonylgruppe ist und n eine ganze Zahl von 1 bis 3 bedeutet,
oder deren Salze,
und die Verbindungen: Ethyl-6-(2,4-dichlorbenzyloxy)-1-(2,4-dichlorphenyl)-methyl-1,4-dihydro-2,4-dioxo-3(2H)-chinazolinacetat und 6-(2,4-Dichlorbenzyloxy)- 1-(2,4-dichlorphenyl)-methyl-1,4-dihydro-2,4-dioxo-3(2H)-chinazolinessigsäure oder deren Salze.

2. Verfahren zur Herstellung der Chinazolin-3-alkancarbonsäurederivate oder deren Salze nach Anspruch 1, **dadurch gekennzeichnet,** daß (a) Verbindungen der allgemeinen Formel (II)

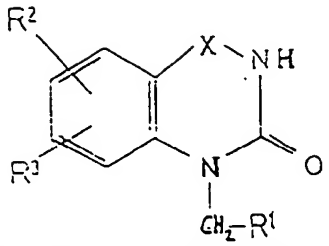


[II]

worin R, R^2, X und n wie in Anspruch 1 definiert sind, oder deren Salze mit Verbindungen der allgemeinen Formel (III)

$$R^1\text{-}CH_2\text{-}Z \qquad (III)$$

worin Z eine Abspaltungsgruppe ist und R^1 wie in Anspruch 1 definiert ist, umgesetzt werden, oder (b) Verbindungen der allgemeinen Formel (IV)

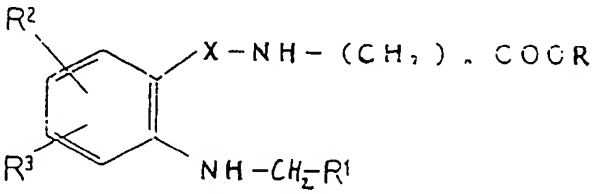


[IV]

worin R^1, R^2, R^3 und X wie in Anspruch 1 definiert sind, oder deren Salze mit Verbindungen der allgemeinen Formel (V),

$$Z\text{-}(CH_2)_n\text{-}COOR \qquad (V)$$

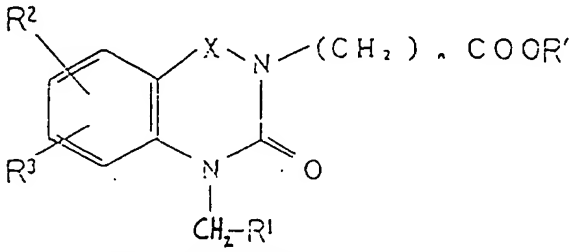
worin Z eine Abspaltungsgruppe ist und R und n wie in Anspruch 1 definiert sind, umgesetzt werden, oder (c) Verbindungen der allgemeinen Formel (VI)



[VI]

worin R, R^1, R^2, R^4, X und n wie in Anspruch 1 definiert sind oder deren Salze mit N,N'-Carbonyldiimidazol umgesetzt werden,

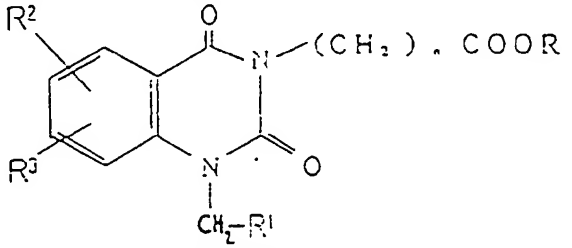
3. Verfahren zur Herstellung der Chinazolin-3-alkancarbonsäurederivate oder deren Salze nach Anspruch 1, worin Rein Wasserstoffatom ist, **dadurch gekennzeichnet,** daß Verbindungen der allgemeinen Formel (VII)



[VII]

worin R' eine Schutzgruppe für die Carboxylgruppe ist und R^1, R^2, R^3, X und n wie in Anspruch 1 definiert sind, hydrolysiert werden.

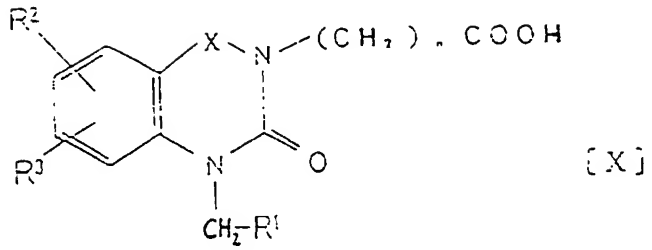
4. Verfahren zur Herstellung der Chinazolin-3-alkancarbonsäurederivate oder deren Salze nach Anspruch 1, worin X eine Thiocarbonylgruppe ist, **dadurch gekennzeichnet,** daß Verbindungen der allgemeinen Formel (IX)



[IX]

worin R, R^1, R^2, R^3 und n wie in Anspruch 1 definiert sind, mit Sulfid umgesetzt werden.

5. Verfahren zur Herstellung der Chinazolin-3-alkancarbonsäurederivate oder deren Salze nach Anspruch 1, worin Reine Schutzgruppe für die Carboxylgruppe ist, **dadurch gekennzeichnet,** daß Verbindungen der allgemeinen Formel (X)



[X]

worin R^1, R^2, R^3, X und n wie in Anspruch 1 definiert sind, mit Verbindungen der allgemeinen Formel (XI)

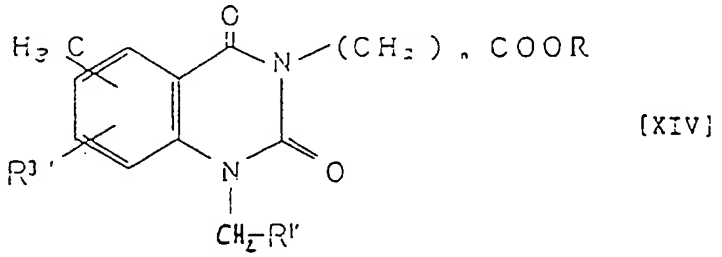
$$R'\text{-}Z \qquad (XI)$$

worin R' eine Schutzgruppe für die Carboxylgruppe ist und Z eine Abspaltungsgruppe ist, in Gegenwart einer geeigneten Base umgesetzt werden oder, nachdem einmal reaktive Derivate der Carbonsäure hergestellt worden sind, dann diese mit Verbindungen der allgemeinen Formel (XII)

$$R'\text{-}OH \qquad (XII)$$

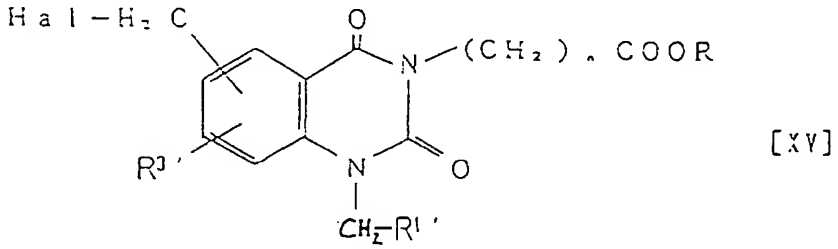
worin R' wie oben beschrieben ist, umgesetzt werden.

6. Verfahren zur Herstellung der Chinazolin-3-alkancarbonsäurederivate oder deren Salze nach Anspruch 1, worin R^2 eine Imidazolylmethylgruppe ist, R^3 Wasserstoff, Halogen oder eine Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen ist und X eine Carbonylgruppe ist, **dadurch gekennzeichnet,** daß mit Chuinazolin-3-alkancarbonsäurederivaten der allgemeinen Formel (XIV)



[XIV]

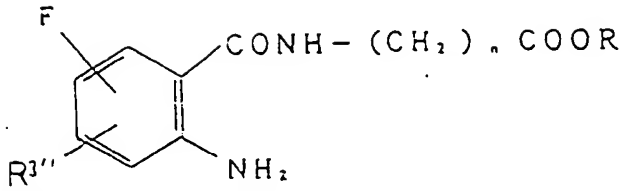
worin $R^{1'}$ eine Phenylgruppe ist (diese Phenylgruppe kann durch ein oder drei aus einer Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen, Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, Halogen, Trifluormethylgruppe, Carboxyethylengruppe oder Ethoxycarbonylethylengruppe substituiert sein), $R^{3'}$ Wasserstoff, Halogen oder eine Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen ist, und R und n wie in Anspruch 1 definiert sind, ein Halogenierungsmittel umgesetzt wird, um Verbindungen der allgemeinen Formel (XV) zu erhalten



[XV]

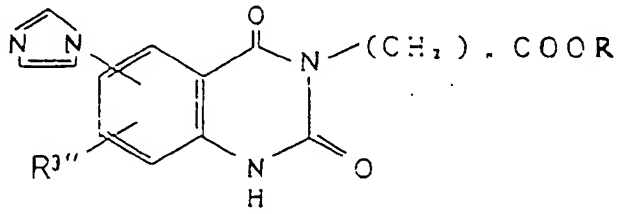
worin Hal Halogen ist und R, $R^{1'}$, $R^{3'}$ und n wie oben beschrieben sind, und diese dann mit Imidazol umgesetzt werden.

7. Verfahren zur Herstellung der Chinazolin-3-alkancarbonsäurederivate oder deren Salze nach Anspruch 1, worin R^2 eine Imidazolylgruppe ist, R^3 Wasserstoff, Halogen, eine Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen, Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, Aralkylgruppe oder Nitrogruppe ist und X eine Carbonylgruppe ist, **dadurch gekennzeichnet,** daß Verbindungen der allgemeinen Formel (XVII)



[XVII]

worin $R^{3''}$ Wasserstoff, Halogen, eine Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen, Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatmen, Aralkylgruppe oder Nitrogruppe ist und R und n wie in Anspruch 1 definiert sind, mit N, N'-Carbonyldiimidazol behandelt werden, um Verbindungen der allgemeinen Formel (XVIII)



[XVIII]

zu erhalten, worin R, $R^{3''}$ und n wie oben beschrieben sind,
und diese dann mit Verbindungen der allgemeine Formel (III)

$$R^1\text{-}CH_2\text{-}Z \qquad \text{(III)}$$

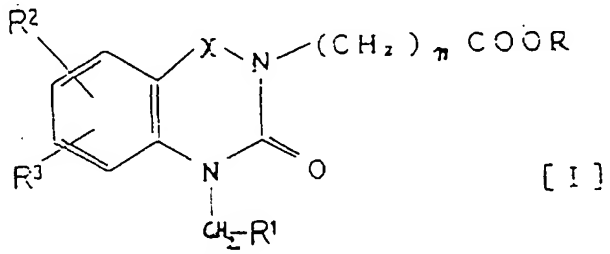
worin Z eine Abspaltungsgruppe ist und R^1 wie in Anspruch 1 definiert ist, umgesetzt werden.

8. Inhibitor der Blutplättchenaggregation, bestehend aus mindestens einer Art von Chinazolin-3-alkancarbonsäurederivaten der allgemeinen Formel (I) oder deren Salzen wie in Anspruch 1 definiert als Wirkstoff(e).

9. Inhibierungsmittel gegenüber Aldosereduktase, bestehend aus mindestens einer Art von Chinazolin-3-alkancarbonsäurederivaten der allgemeinen Formel (I) oder deren Salzen wie in Anspruch 1 definiert als Wirkstoff(e).

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung von Chinazolin-3-alkancarbonsäurederivaten oder deren Salzen der allgemeinen Formel (I)

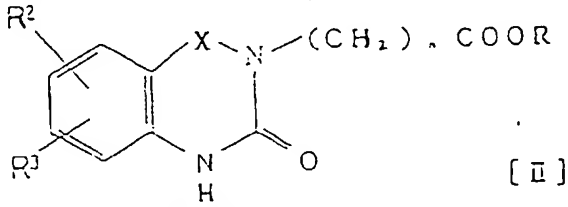


[I]

worin RWasserstoff oder eine Schutzgruppe für die Carboxylgruppe ist, R^1 eine Phenylgruppe ist, welche durch eine bis drei aus einer Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen, Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, Halogen, Trifluormethylgruppe, Carboxyethylengruppe oder Ethoxycarbonylethylengruppe substituiert sein kann, R^2 und R^3, welche gleich oder voneinander verschieden sind, jeweils Wasserstoff, Halogen, eine Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen, Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, Aralkylgruppe, Nitrogruppe, Imidazolylgruppe, Imidazolylmethylgruppe oder

(worin R^4 und R^5, welche gleich oder voneinander verschieden sind, jeweils Wasserstoff oder eine Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeuten oder miteinander verbunden sind zur Bildung einer 5- oder 6-gliedrigen heterocyclischen Gruppe, welche weitere Heteroatome enthalten kann) bedeuten, X eine Carbonyl- oder

Thiocarbonylgruppe ist und n eine ganze Zahl von 1 bis 3 bedeutet,
und zur Herstellung der Verbindungen: Ethyl-6-(2,4-dichlorbenzyloxy)1-(2,4-dichlorphenyl)-methyl-1,4-dihydro-2,4-dioxo-3(2H)-chinazolinacetat und 6-(2,4-Dichlorbenzyloxy)-1-(2,4-dichlorphenyl)-methyl-1,4-dihydro-2,4-dioxo-3(2H)-chinazolinessigsäure oder deren Salze,
dadurch gekennzeichnet, daß (a) Verbindungen der allgemeinen Formel (II)

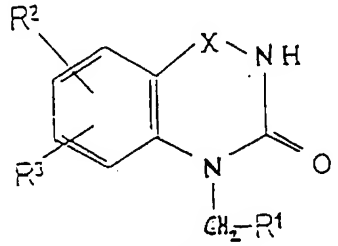


[II]

worin R, R^2, X und n wie oben definiert sind, oder deren Salze mit Verbindungen der allgemeinen Formel (III)

$$R^1\text{-}CH_2\text{-}Z \qquad \text{(III)}$$

worin Z eine Abspaltungsgruppe ist und R^1 wie oben definiert ist, umgesetzt werden, oder (b) Verbindungen der allgemeinen Formel (IV)

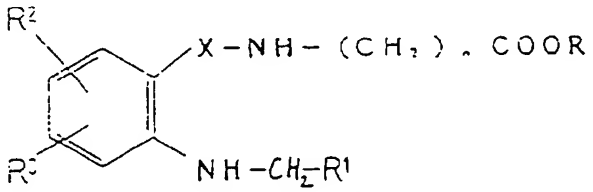


[IV]

worin R^1, R^2, R^3 und X wie oben definiert sind, oder deren Salze mit Verbindungen der allgemeinen Formel (V),

$$Z\text{-}(CH_2)_n\text{-}COOR \qquad \text{(V)}$$

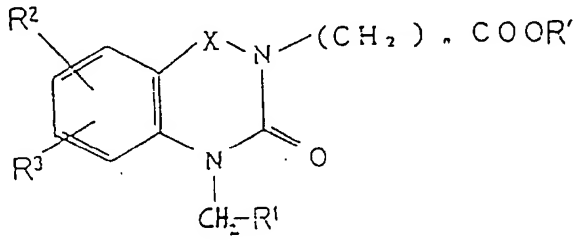
worin Z eine Abspaltungsgruppe ist und R und n wie oben definiert sind, umgesetzt werden, oder (c) Verbindungen der allgemeinen Formel (VI)



[VI]

worin R, R^1, R^2, R^4, X und n wie oben definiert sind, oder deren Salze mit N,N'-Carbonyldiimidazol umgesetzt werden.

2. Verfahren zur Herstellung der Chinazolin-3-alkancarbonsäurederivate oder deren Salze nach Anspruch 1, worin R ein Wasserstoffatom ist, **dadurch gekennzeichnet,** daß Verbindungen der allgemeinen Formel (VII)

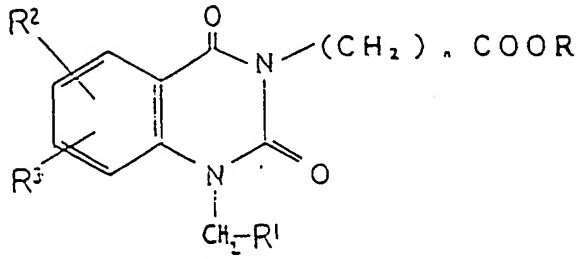


[VII]

worin R' eine Schutzgruppe für die Carboxylgruppe ist und R^1, R^2, R^3, X und n wie in Anspruch 1 definiert sind, hydrolysiert werden.

3. Verfahren zur Herstellung der Chinazolin-3-alkancarbonsäurederivate oder deren Salze nach Anspruch 1, worin

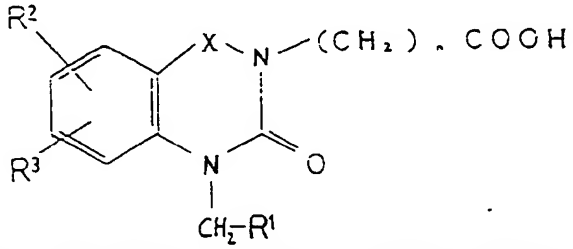
X eine Thiocarbonylgruppe ist, **dadurch gekennzeichnet,** daß Verbindungen der allgemeinen Formel (IX)



[IX]

worin R, R^1, R^2, R^3 und n wie in Anspruch 1 definiert sind, mit Sulfid umgesetzt werden.

4. Verfahren zur Herstellung der Chinazolin-3-alkancarbonsäurederivate oder deren Salze nach Anspruch 1, worin Reine Schutzgruppe für die Carboxylgruppe ist, **dadurch gekennzeichnet,** daß Verbindungen der allgemeinen Formel (X)



[X]

worin R^1, R^2, R^3, X und n wie in Anspruch 1 definiert sind, mit Verbindungen der allgemeinen Formel (XI)

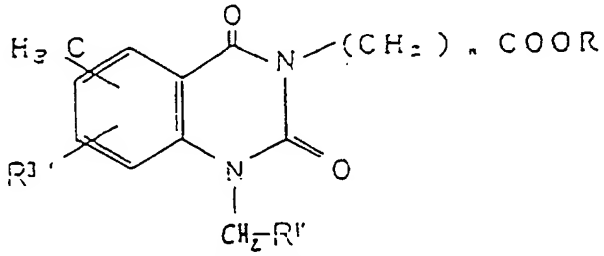
R'-Z (XI)

worin R' eine Schutzgruppe für die Carboxylgruppe ist und Z eine Abspaltungsgruppe ist, in Gegenwart einer geeigneten Base umgesetzt werden oder, nachdem einmal reaktive Derivate der Carbonsäure hergestellt worden sind, dann diese mit Verbindungen der allgemeinen Formel (XII)

R'-OH (XII)

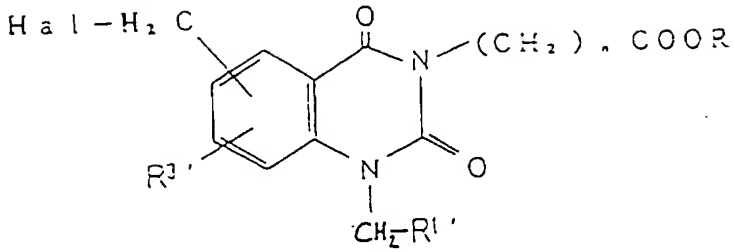
worin R' wie oben beschrieben ist, umgesetzt werden.

5. Verfahren zur Herstellung der Chinazolin-3-alkancarbonsäurederivate oder deren Salze nach Anspruch 1, worin R^2 eine Imidazolylmethylgruppe ist, R^3 Wasserstoff, Halogen oder eine Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen ist und X eine Carbonylgruppe ist, **dadurch gekennzeichnet,** daß mit Chuinazolin-3-alkancarbonsäurederivaten der allgemeinen Formel (XIV)



[XIV]

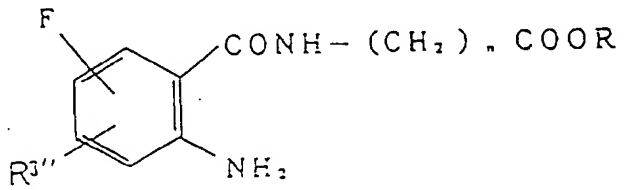
worin $R^{1'}$ eine Phenylgruppe ist (diese Phenylgruppe kann durch ein oder drei aus einer Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen, Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, Halogen, Trifluormethylgruppe, Carboxyethylengruppe oder Ethoxycarbonylethylengruppe substituiert sein), $R^{3'}$ Wasserstoff, Halogen oder eine Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen ist, und R und n wie in Anspruch 1 definiert sind, ein Halogenierungsmittel umgesetzt wird, um Verbindungen der allgemeinen Formel (XV) zu erhalten



[XV]

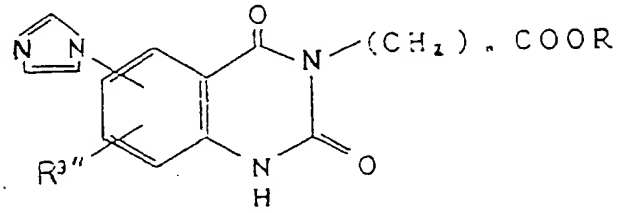
worin Hal Halogen ist und R, R1', R3' und n wie oben beschrieben sind, und diese dann mit Imidazol umgesetzt werden.

6. Verfahren zur Herstellung der Chinazolin-3-alkancarbonsäurederivate oder deren Salze nach Anspruch 1, worin R^2 eine Imidazolylgruppe ist, R^3 Wasserstoff, Halogen, eine Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen, Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, Aralkylgruppe oder Nitrogruppe ist und X eine Carbonylgruppe ist, **dadurch gekennzeichnet,** daß Verbindungen der allgemeinen Formel (XVII)



[XVII]

worin $R^{3''}$ Wasserstoff, Halogen, eine Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen, Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatmen, Aralkylgruppe oder Nitrogruppe ist und R und n wie in Anspruch 1 definiert sind, mit N, N'-Carbonyldiimidazol behandelt werden, um Verbindungen der allgemeinen Formel (XVIII)



[XVIII]

zu erhalten, worin R, $R^{3''}$ und n wie oben beschrieben sind,
und diese dann mit Verbindungen der allgemeine Formel (III)

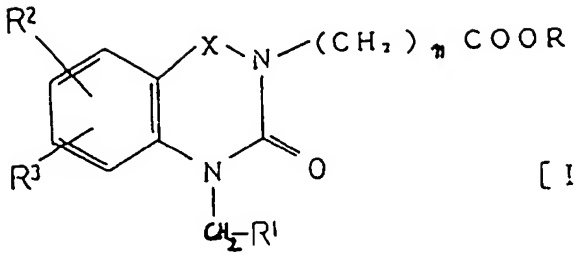
$$R^1\text{-}CH_2\text{-}Z \qquad \text{(III)}$$

worin Z eine Abspaltungsgruppe ist und R^1 wie in Anspruch 1 definiert ist, umgesetzt werden.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, LI, DE, FR, GB, IT, NL, SE

1. Dérivés d'acide quinazoline-3-alcanoïque correspondant à la formule générale (I) :

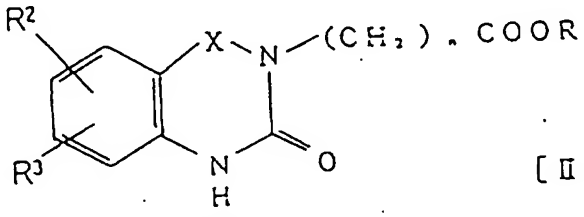


[I]

dans laquelle R représente un atome d'hydrogène ou un groupe protecteur du groupe carboxyle, R^1 représente un groupe phényle qui peut être substitué avec de 1 à 3 groupes alkyle inférieurs comportant de 1 à 6 atomes de carbone, groupes alkoxy inférieurs comportant de 1 à 3 atomes de carbone, atomes d'halogène, groupes trifluorométhyle, groupes carboxyéthylène ou groupes éthoxy-carbonyléthylène, R^2 et R^3 qui sont identiques ou différents l'un de l'autre, représentent chacun un atome d'hydrogène, un atome d'halogène, un groupe alkyle inférieur comportant de 1 à 6 atomes de carbone, un groupe alkoxy inférieur comportant de 1 à 3 atomes de carbone, un groupe aralkyle, un groupe nitro, un groupe imidazolyle, un groupe imidazolylméthyle ou

(R^4 et R^5 qui sont identiques ou différents l'un de l'autre, représentant chacun un atome d'hydrogène ou un groupe alkyle inférieur comportant de 1 à 6 atomes de carbone, ou ils sont reliés entre eux pour former un groupe hétérocyclique à cinq ou six chaînons pouvant contenir d'autres hétéroatomes), X représente un groupe carbonyle ou thiocarbonyle, et n représente un entier de 1 à 3, ainsi que les composés suivant : le 6-(2,4-dichlorobenzyloxy)-1-(2,4-dichlorophényl)méthyl-1,4-dihydro-2,4-dioxo-3(2H)quinazoline acétate d'éthyle et l'acide 6-(2,4-dichlorobenzyloxy)-1-(2,4-dichlorophényl)méthyl-1,4-dihydro-2,4-dioxo-3(2H)quinazoline acétique ou leurs sels.

2. Procédé de préparation de dérivés d'acide quinazoline-3-alcanoïque ou de leurs sels selon la revendication 1, caractérisé en ce que (a) on fait réagir des composés représentés par la formule générale (II) :

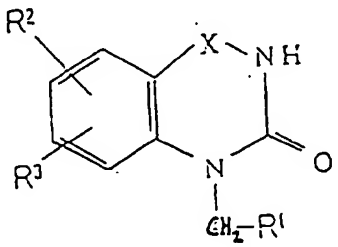


[II]

dans laquelle R, R^2, R^3, X et n sont tels que définis dans la revendication 1, ou leurs sels, avec des composés de formule générale (III) :

$$R^1\text{-}CH_2\text{-}Z \qquad \text{(III)}$$

dans laquelle Z représente un groupe éliminable et R^1 est tel que défini dans la revendication 1, ou (b) on fait réagir des composés représentés par la formule générale (IV) :



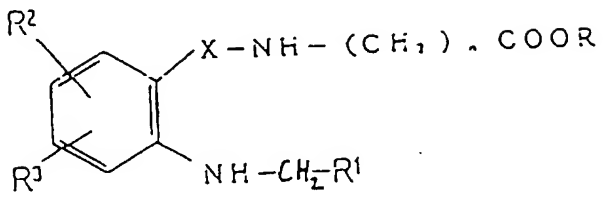
[IV]

dans laquelle R^1, R^2, R^3 et X sont tels que définis dans la revendication 1, ou leurs sels, avec des composés de formule générale (V) :

$$Z\text{-}(CH_2)n\text{-}COOR \qquad \text{(V)}$$

dans laquelle Z représente un groupe éliminable, et R et n sont tels que définis dans la revendication 1, ou (c) on

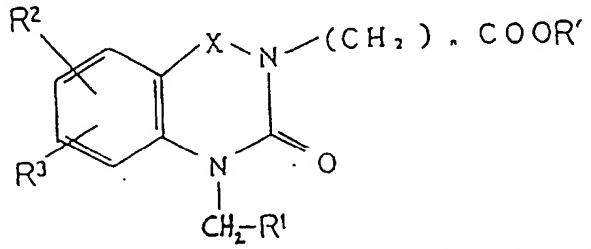
fait réagir des composés de formule générale (VI) :



[VI]

dans laquelle R, R^1, R^2, R^4, X et n sont tels que définis dans la revendication 1, ou leurs sels, avec du N,N'-carbonyldiimidazole.

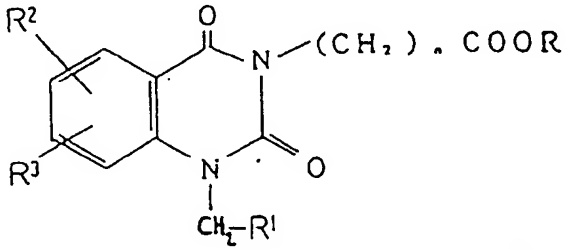
3. Procédé de préparation de dérivés d'acide quinazoline-3-alcanoïque ou de leurs sels, selon la revendication 1, dans lesquels R représente un atome d'hydrogène, caractérisé en ce qu'on hydrolyse des composés représentés par la formule générale (VII) :



[VII]

dans laquelle R' représente un groupe protecteur du groupe carboxyle, et R^1, R^2, R^3, X et n sont tels que définis dans la revendication 1.

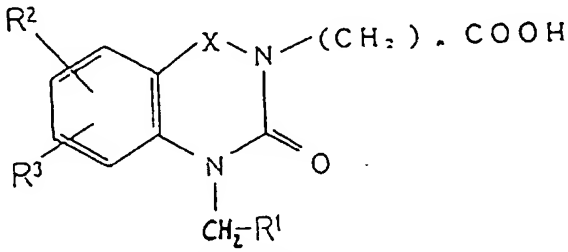
4. Procédé de préparation de dérivés d'acide quinazoline-3-alcanoïque ou de leurs sels selon la revendication 1, dans lesquels X représente un groupe thiocarbonyle, caractérisé en ce qu'on fait réagir des composés de formule générale (IX) :



[IX]

dans laquelle R, R^1, R^2, R^3 et n sont tels que définis dans la revendication 1, avec un sulfure.

5. Procédé de préparation de dérivés d'acide quinazoline-3-alcanoïque ou de leurs sels selon la revendication 1, dans lesquels R représente un groupe protecteur du groupe carboxyle, caractérisé en ce qu'on fait réagir des composés représentés par la formule générale (X) :



[X]

dans laquelle R^1, R^2, R^3, X et n sont tels que définis dans la revendication 1, avec des composés de formule générale (XI) :

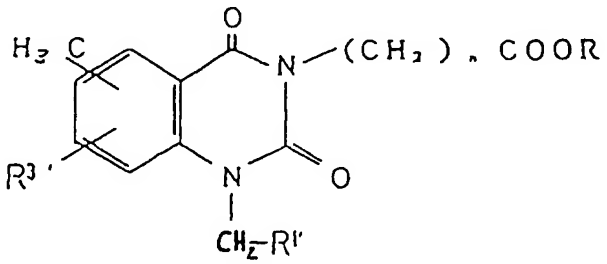
R'-Z (XI)

dans laquelle R' représente un groupe protecteur du groupe carboxyle, et Z représente un groupe éliminable, en présence d'une base appropriée, ou, après avoir produit des dérivés réactifs d'acide carboxylique, on les fait ensuite réagir avec des composés de formule générale (XII) :

R'-OH (XII)

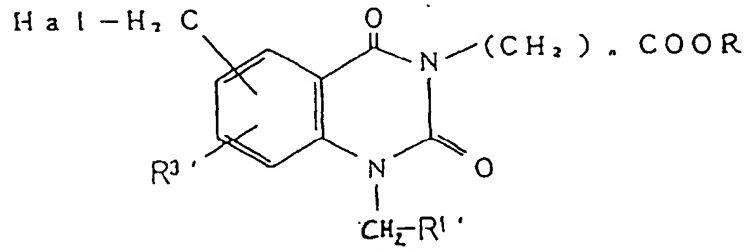
dans laquelle R' est tel que défini ci-dessus.

6. Procédé de préparation de dérivés d'acide quinazoline-3-alcanoïque ou de leurs sels selon la revendication 1, dans lesquels R^2 représente un groupe imidazolylméthyle, R^3 représente un atome d'hydrogène, d'halogène ou un groupe alkoxy inférieur comportant de 1 à 3 atomes de carbone, et X représente un groupe carbonyle, caractérisé en ce qu'on fait réagir un agent d'halogénation avec des dérivés d'acide quinazoline-3-alcanoïque représentés par la formule générale (XIV) :



[XIV]

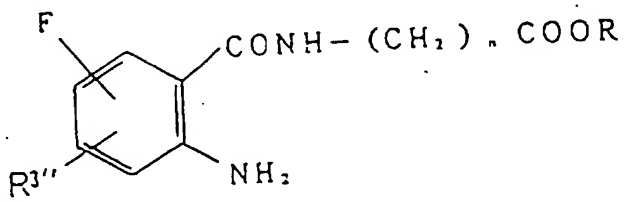
dans laquelle $R^{1'}$ représente un groupe phényle (ce groupe phényle pouvant être substitué avec de 1 à 3 groupes alkyle inférieurs comportant de 1 à 6 atomes de carbone, groupes alkoxy inférieurs comportant de 1 à 3 atomes de carbone, atomes d'halogène, groupes trifluorométhyle, groupes carboxyéthylène ou groupes éthoxycarbonyléthylène), $R^{3'}$ représente un atome d'hydrogène, d'halogène ou un groupe alkoxy inférieur comportant de 1 à 3 atomes de carbone, et R ainsi que n sont tels que définis dans la revendication 1, pour obtenir des composés de formule générale (XV) :



[XV]

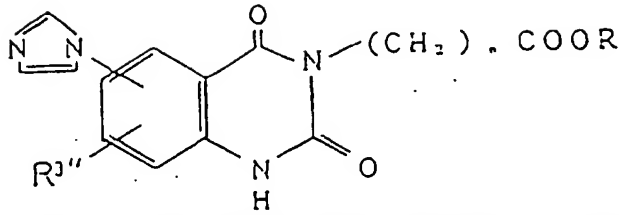
dans laquelle Hal représente un atome d'halogène, et R, $R^{1'}$, $R^{3'}$ et n sont tels que définis ci-dessus, et on les fait ensuite réagir avec un imidazole.

7. Procédé de préparation de dérivés d'acide quinazoline-3-alcanoïque ou de leurs sels selon la revendication 1, dans lesquels R^2 représente un groupe imidazolyle, R^3 représente un atome d'hydrogène, d'halogène, un groupe alkyle inférieur comportant de 1 à 6 atomes de carbone, un groupe alkoxy inférieur comportant de 1 à 3 atomes de carbone, un groupe aralkyle ou un groupe nitro, et X représente un groupe carbonyle, caractérisé en ce qu'on traite des composés de formule générale (XVII) :



[XVII]

dans laquelle $R^{3''}$ représente un atome d'hydrogène, d'halogène, un groupe alkyle inférieur comportant de 1 à 6 atomes de carbone, un groupe alkoxy inférieur comportant de 1 à 3 atomes de carbone, un groupe aralkyle ou un groupe nitro, et R et n sont tels que définis dans la revendication 1, avec du N,N'-carbonyldiimidazole pour obtenir des composés de formule générale (XVIII) :



[XVIII]

dans laquelle R, $R^{3''}$ et n sont tels que définis ci-dessus, et on les fait ensuite réagir avec des composés de formule générale (III) :

$$R^1\text{-}CH_2\text{-}Z \qquad \text{(III)}$$

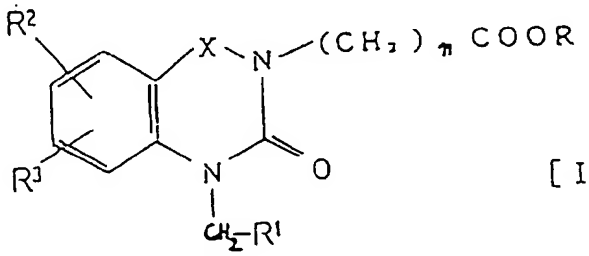
dans laquelle Z représente un groupe éliminable, et R^1 est tel que défini dans la revendication 1.

8. Inhibiteur d'agrégation de plaquettes consistant en au moins un type de dérivé d'acide quinazoline-3-alcanoïque représenté par la formule générale (I) ou de sels de celui-ci, ainsi que cela est défini dans la revendication 1, en tant qu'un ou plusieurs ingrédients efficaces.

9. Agent inhibiteur de l'aldose réductase consistant en au moins un type de dérivé d'acide quinazoline-3-alcanoïque représenté par la formule générale (I) ou de sels de celui-ci ainsi que cela est défini dans la revendication 1, en tant qu'un ou plusieurs ingrédients efficaces.

Revendications pour l'Etat contractant suivant : ES

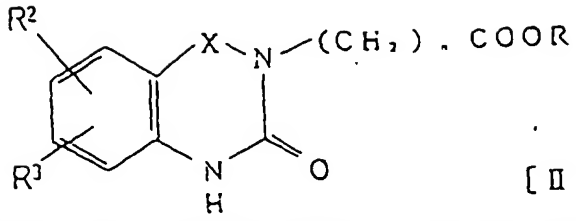
1. Procédé de préparation de dérivés d'acide quinazoline-3-alcanoïque ou de leurs sels représentés par la formule générale (I) :



[I]

dans laquelle R représente un atome d'hydrogène ou un groupe protecteur du groupe carboxyle, R^1 représente un groupe phényle qui peut être substitué avec 1 à 3 groupes alkyle inférieurs comportant de 1 à 6 atomes de carbone, groupes alkoxy inférieurs comportant de 1 à 3 atomes de carbone, atomes d'halogène, groupes trifluorométhyle, groupes carboxyéthylène ou groupes éthoxycarbonyléthylène, R^2 et R^3 qui sont identiques ou différents l'un de l'autre, représentent chacun un atome d'hydrogène, d'halogène, un groupe alkyle inférieur comportant de 1 à 6 atomes de carbone, un groupe alkoxy inférieur comportant de 1 à 3 atomes de carbone, un groupe aralkyle, un groupe nitro, un groupe imidazolyle, un groupe imidazolylméthyle ou

(R^4 et R^5 qui sont identiques ou différents l'un de l'autre, représentant chacun un atome d'hydrogène ou un groupe alkyle inférieur comportant de 1 à 6 atomes de carbone, ou ils sont reliés entre eux pour former un groupe hétérocyclique à cinq ou six chaînons pouvant contenir d'autres hétéroatomes), X représente un groupe carbonyle ou thiocarbonyle, et n représente un entier de 1 à 3, et de préparation des composés suivant : le 6-(2,4-dichlorobenzyloxy)-1-(2,4-dichlorophényl)méthyl-1,4-dihydro-2,4-dioxo-3(2H)quinazoline acétate d'éthyle et l'acide 6-(2,4-dichlorobenzyloxy)-1-(2,4-dichlorophényl)méthyl-1,4-dihydro-2,4-dioxo-3(2H)quinazoline acétique, caractérisé en ce que (a) on fait réagir des composés représenté par la formule générale (II) :

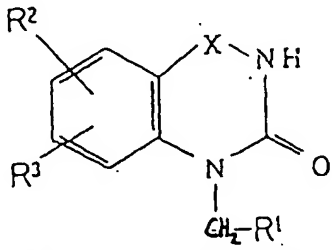


[II]

dans laquelle R, R^2, R^3, X et n sont tels que définis ci-dessus, ou leurs sels, avec des composés de formule générale (III) :

$$R^1\text{-}CH_2\text{-}Z \qquad \text{(III)}$$

dans laquelle Z représente un groupe éliminable, et R^1 est tel que défini ci-dessus, ou (b) on fait réagir des composés de formule générale (IV) :

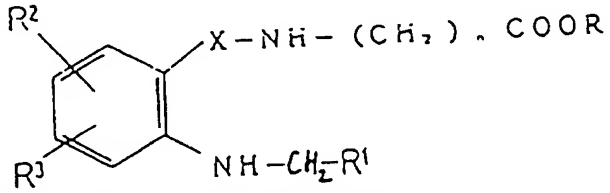


[IV]

dans laquelle R^1, R^2, R^3 et X sont tels que définis ci-dessus, ou leurs sels, avec des composés de formule générale (V) :

$$Z\text{-}(CH_2)n\text{-}COOR \qquad \text{(V)}$$

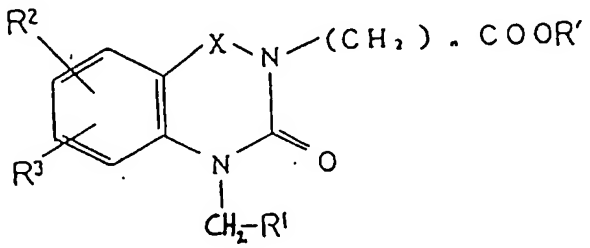
dans laquelle Z représente un groupe éliminable, et R ainsi que n sont tels que définis ci-dessus, ou (c) on fait réagir des composés de formule générale (VI) :



[VI]

dans laquelle R, R^1, R^2, R^4, X et n sont tels que définis ci-dessus, ou leurs sels, avec du N,N'-carbonyldiimidazole.

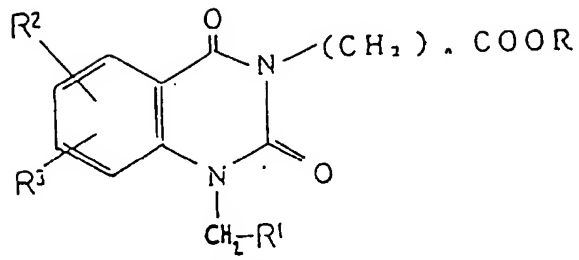
2. Procédé de préparation de dérivés d'acide quinazoline-3-alcanoïque ou de leurs sels, selon la revendication 1, dans lesquels R représente un atome d'hydrogène, caractérisé en ce que l'on hydrolyse des composés de formule générale (VII) :



[VII]

dans laquelle R' représente un groupe protecteur du groupe carboxyle, et R^1, R^2, R^3, X et n sont tels que définis dans la revendication 1.

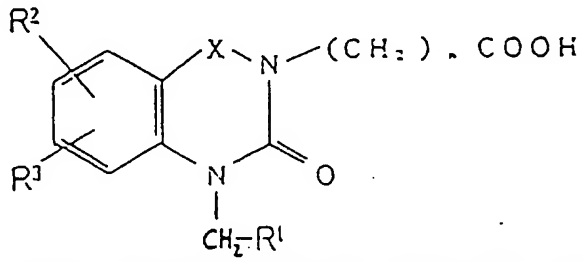
3. Procédé de préparation de dérivés d'acide quinazoline-3-alcanoïque ou de leurs sels selon la revendication 1, dans lesquels X représente un groupe thiocarbonyle, caractérisé en ce qu'on fait réagir des composés de formule générale (IX) :



[IX]

dans laquelle R, R^1, R^2, R^3 et n sont tels que définis dans la revendication 1, avec un sulfure.

4. Procédé de préparation de dérivés d'acide quinazoline-3-alcanoïque ou de leurs sels selon la revendication 1, dans lesquels R représente un groupe protecteur du groupe carboxyle, caractérisé en ce que l'on fait réagir des composés de formule générale (X) :



[X]

dans laquelle R^1, R^2, R^3, X et n sont tels que définis dans la revendication 1, avec des composés de formule générale (XI) :

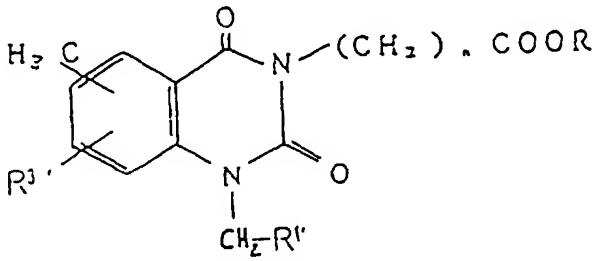
$$R'\text{-}Z \qquad (XI)$$

dans laquelle R' représente un groupe protecteur du groupe carboxyle, et Z représente un groupe éliminable, en présence d'une base appropriée, ou après production de dérivés réactifs d'acide carboxylique, on les fait ensuite réagir avec des composés de formule générale (XII) :

$$R'\text{-}OH \qquad (XII)$$

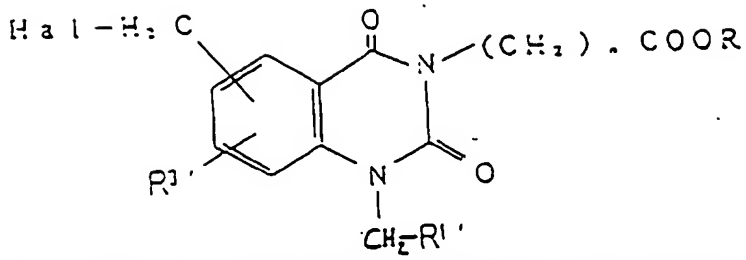
dans laquelle R' est tel que défini ci-dessus.

5. Procédé de préparation de dérivés d'acide quinazoline-3-alcanoïque ou de leurs sels selon la revendication 1, dans lesquels R^2 représente un groupe imidazolylméthyle, R^3 représente un atome d'hydrogène, d'halogène ou un groupe alkoxy inférieur comportant de 1 à 3 atomes de carbone, et X représente un groupe carbonyle, caractérisé en ce qu'on fait réagir un agent d'halogénation avec des dérivés d'acide quinazoline-3-alcanoïque représentés par la formule générale (XIV) :



[XIV]

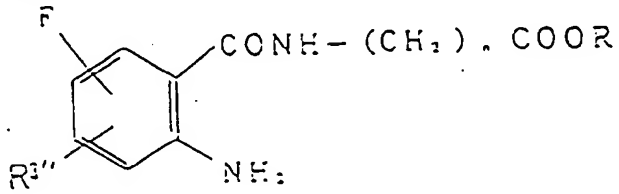
dans laquelle $R^{1'}$ représente un groupe phényle (ce groupe phényle couvant erre substitué avec de 1 à 3 groupes alkyle inférieurs comportant de 1 à 6 atomes de carbone, groupes alkoxy inférieurs comportant de 1 à 3 atomes de carbone, atomes d'halogène, groupes trifluorométhyle, groupes carboxyéthylène ou groupes éthoxycarbonyléthylène), $R^{3'}$ représente un atome d'hydrogène, d'halogène ou un groupe alkoxy inférieur comportant de 1 à 3 atomes de carbone, et R ainsi que n sont tels que définis dans la revendication 1, pour obtenir des composés de formule générale (XV) :



[XV]

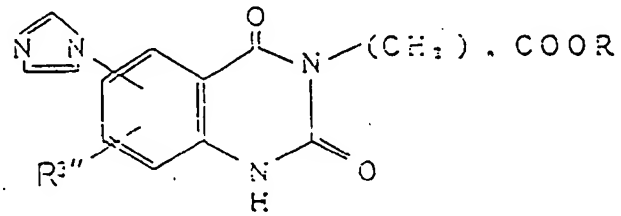
dans laquelle Hal représente un atome d'halogène, et R, $R^{1'}$, $R^{3'}$ et n sont tels que définis ci-dessus, et on les fait ensuite réagir avec un imidazole.

6. Procédé de préparation de dérivés d'acide quinazoline-3-alcanoïque ou de leurs sels selon la revendication 1, dans lesquels R^2 représente un groupe imidazolyle, R^3 représente un atome d'hydrogène, d'halogène, un groupe alkyle inférieur comportant de 1 à 6 atomes de carbone, un groupe alkoxy inférieur comportant de 1 à 3 atomes de carbone, un groupe aralkyle ou un groupe nitro, et X représente un groupe carbonyle, caractérisé en ce qu'on traite des composés de formule générale (XVII) :



[XVII]

dans laquelle $R^{3''}$ représente un atome d'hydrogène, d'halogène, un groupe alkyle inférieur comportant de 1 à 6 atomes de carbone, un groupe alkoxy inférieur comportant de 1 à 3 atomes de carbone, un groupe aralkyle ou un groupe nitro, et R et n sont tels que définis dans la revendication 1, avec du N,N'-carbonyldiimidazole pour obtenir des composés de formule générale (XVIII) :



[XVIII]

dans laquelle R, $R^{3''}$ et n sont tels que définis ci-dessus, et on les fait ensuite réagir avec des composés de formule générale (III) :

$$R^1\text{-}CH_2\text{-}Z \qquad \text{(III)}$$

dans laquelle Z représente un groupe éliminable, et R^1 est tel que défini dans la revendication 1..